Cancer Treatment Reports

A Publication of the National Cancer Institute

Volume 71
Number 11
November 1987

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service National Institutes of Health

Cancer Treatment Reports

National Cancer Institute, Vincent T. DeVita, Jr, ***Director***

NOTICE:

***Cancer Treatment Reports* is no longer considering new manuscripts for publication. New submissions will be returned to authors without review.**

International Cancer Information Center
Susan Molloy Hubbard, ***Director***

Publications Branch
Robin A. Atkiss, ***Chief***

Robert E. Wittes, ***Editor-In-Chief***
Elaine Price Beck, ***Acting Managing Editor***

Editorial Board

Joseph Aisner
Lewis Aronow
Gregory Curt
Richard L. Cysyk
Ross C. Donehower
Michael Friedman
Timothy J. Kinsella
Robert F. Ozols
Carl Pinsky
David G. Poplack
Richard Simon

Advisory Board

Charles M. Balch
Robert C. Bast, Jr
Gianni Bonadonna
Edwin C. Cadman
Giulio J. D'Angio
I. David Goldman
Heine H. Hansen
Simon Kramer
Susan E. Krown
John E. Niederhuber
T. L. Phillips
H. M. Pinedo
Carol S. Portlock
Joseph V. Simone
Samuel A. Wells, Jr

Editorial Staff

Editor:
Mary Olvey Cowgill

Editorial Assistant:
Julia Redmond

Manuscript Office:
Olga Sisson

Manuscripts

All inquiries concerning the status of manuscripts should be addressed to: Managing Editor, Cancer Treatment Reports, R. A. Bloch International Cancer Information Center, Bldg 82, Rm 231, National Cancer Institute, Bethesda, MD 20892 (301-496-6975).

Copyright

All material published in this journal is in the public domain; therefore, permission to reproduce any portion is not necessary. As a matter of courtesy, contact should be made with the author concerned.

Subscriptions

The subscriber service desk of the U.S. Government Printing Office may be reached directly at (202) 275-3054 for any questions concerning individual subscriptions.

The Secretary of Health and Human Services has determined that the publication of this periodical is necessary in the transaction of the public business by law of this Department. Use of funds for printing this periodical has been approved by the Director of the Office of Management and Budget.

INSTRUCTIONS TO AUTHORS

Title Page
Includes complete title of the manuscript and the full name, affiliation, and address of each author. Indicate full name and address of author to whom correspondence and/or reprint requests are to be sent.

Summary
Begin the article with a short summary.

Text
Submit an original and 3 copies of the manuscript, typed double-spaced. Number each page consecutively. Dot-matrix or italicized texts will not be accepted. Use accepted spelling, abbreviation, and hyphenation found in *Webster's New International Dictionary*. Footnotes should be typed at the bottom of the page on which they appear.

Tables
Submit each table on a separate page, typed double-spaced. Please use only standard abbreviations; otherwise use full words.

References
Submit references typed double-spaced. Follow the standard form of *Index Medicus:* author, title, name of journal, volume number, page or inclusive pages, and year. In book references give author, chapter title, book title, city and name of publisher, date of publication, volume number, and pages cited. References in text should begin with number 1 and continue consecutively. References to papers published in meeting proceedings should include author; title of paper; title of meeting; city and name of publisher; date of publication; volume number; and pages. Papers presented at meetings but not published should be cited in a footnote rather than in the reference section.

Illustrations
Photographs and graphs should be clear, glossy prints. If original artwork is submitted, it should be done in black ink for good reproduction. Please send 2 copies of each print. Photocopies reproduce poorly. Color photographs or transparencies are acceptable.

Nomenclature
Names of compounds should conform to American usage. See *USAN and the USP Dictionary of Drug Names* or *The Merck Index* for proper nomenclature.

Brief Reports
Manuscripts published in the Brief Reports section should be no longer than 5 double-spaced pages including references, tables, and a short summary; illustrations are usually omitted.

Clinical Trials Summaries
Manuscripts published in this section should be no longer than 300 words and should be submitted with no more than 1 table and 5 references, and no illustrations. Tables should include: *patient characteristics and prognostic factors* (age/sex, performance status, stage of disease, pathologic types of disease, prior therapy), *drug regimen*, or *standardized toxicity grades* to demonstrate that an appropriate, biologically active dose was administered.

Letters to the Editor
Letters to the Editor should be no longer than 3 double-spaced text pages and should be submitted with no more than 1 table and 5 references; figures are usually omitted.

Reprints
Supplied free of charge, 100 reprints (approximately 20 reprints for Letters to the Editor) will be sent to the senior or specified author about 3 weeks after publication of the article.

Announcements
Announcements of meetings are accepted for publication free of charge. Mail to: Editorial Office, Cancer Treatment Reports, R. A. Bloch International Cancer Information Center, Bldg 82, Rm 231, National Institutes of Health, Bethesda, MD 20892. Allow 4 months for publication.

METHODOLOGIC GUIDELINES FOR REPORTS OF CLINICAL TRIALS*

1. Authors should discuss briefly the quality control methods used to ensure that the data are complete and accurate. A reliable procedure should be cited for ensuring that all patients entered on study are actually reported upon. If no such procedures are in place, their absence should be noted. Any procedures employed to ensure that assessment of major endpoints is reliable should be mentioned (eg, second-party review of responses) or their absence noted.

2. All patients registered on study should be accounted for. The report should specify for each treatment the number of patients who were not eligible, who died or withdrew before treatment began. The distribution of follow-up times should be described for each treatment, and the number of patients lost to follow-up should be given.

3. The study should not have an inevaluability rate for major endpoints of greater than 15%. Not more than 15% of eligible patients should be lost to follow-up or considered inevaluable for response due to early death, protocol violation, missing information, etc.

4. In randomized studies, the report should include a comparison of survival and/or other major endpoints for all eligible patients as randomized, that is, with no exclusions other than those not meeting eligibility criteria.

5. The sample size should be sufficient to either establish or conclusively rule out the existence of effects of clinically meaningful magnitude. For "negative" results in therapeutic comparisons, the adequacy of sample size should be demonstrated by either presenting confidence limits for true treatment differences or calculating statistical power for detecting differences. For uncontrolled phase II studies, a procedure should be in place to prevent the accrual of an inappropriately large number of patients, when the study has shown the agent to be inactive.

6. Authors should state whether there was an initial sample size and, if so, what it was. They should specify how frequently interim analyses were performed and how the decisions to stop accrual and report results were arrived at.

7. All claims of therapeutic efficacy should be based upon explicit comparison with a specific control group, except in special circumstances where each patient is his own control. If nonrandomized controls are used, the characteristics of the patients should be presented in detail and compared to those of the experimental group. Potential sources of bias should be adequately discussed. Comparison of survival between responders and nonresponders does not establish efficacy and should not generally be included. Reports of phase II trials which draw conclusions about antitumor activity but not therapeutic efficacy generally do not require a control group.

8. The patients studied should be adequately described. Applicability of conclusions to other patients should be carefully dealt with. Claims of subset-specific treatment differences must be carefully documented statistically as more than the random results of multiple-subset analyses.

9. The methods of statistical analysis should be described in detail sufficient that a knowledgeable reader could reproduce the analysis if the data were available.

**From* Methodologic Guidelines for Reports of Clinical Trials (Cancer Treat Rep 69:1-3, 1985).

Contents

Cancer Treatment Reports
Volume 71, Number 11
November 1987

ORIGINAL ARTICLES

997 Dacarbazine, Vindesine, and Cisplatin Combination Chemotherapy in Advanced Malignant Melanoma: A Phase II Study. **S. Gundersen.** The Norwegian Radium Hospital, Montebello, Oslo, Norway

1001 Continuous 5-Day Infusion of Vinblastine for Percutaneous Hepatic Arterial Chemotherapy for Metastatic Breast Cancer. **G. Fraschini, G. Fleishman, C. Charnsangavej, C. H. Carrasco, and G. N. Hortobagyi.** The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston

1007 Randomized, Double-Blind, Cross-Over Study Comparing Prochlorperazine and Lorazepam With High-Dose Metoclopramide and Lorazepam for the Control of Emesis in Patients Receiving Cytotoxic Chemotherapy. **J. F. Bishop, M. Wolf, J. P. Matthews, K. Scott, S. Ackland, K. Yuen, C. Morton, B. L. Hillcoat, and I. A. Cooper.** Peter MacCallum Cancer Institute, Melbourne, Australia

1013 Preliminary Report on the Treatment of Esophageal Cancer by Intraluminal Microwave Hyperthermia and Chemotherapy. **D.-J. Li and B.-S. Hou.** Henan Tumor Institute, Zhengzhou, Peoples Republic of China

1021 Comparison of the Actions of the Antiprogestin Mifepristone (RU486), the Progestin Megestrol Acetate, the LHRH Analog Buserelin, and Ovariectomy in the Treatment of Rat Mammary Tumors. **G. H. Bakker, B. Setyono-Han, M. S. Henkelman, F. H. de Jong, S. W. J. Lamberts, P. van der Schoot, and J. G. M. Klijn.** The Dr. Daniel den Hoed Cancer Center and Erasmus University, Rotterdam, The Netherlands

1029 High-Dose Pulse Chlorambucil in Advanced, Low-Grade Non-Hodgkin's Lymphoma. **C. S. Portlock, D. S. Fischer, E. Cadman, W. B. Lundberg, A. Levy, S. Bobrow, J. R. Bertino, and L. Farber.** Yale University School of Medicine, New Haven, Connecticut

1033 Improved Survival of Infants Less Than 1 Year of Age With Acute Lymphoblastic Leukemia Treated With Intensive Multiagent Chemotherapy. **G. H. Reaman, P. G. Steinherz, P. S. Gaynon, W. A. Bleyer, J. Z. Finklestein, R. Evans, D. R. Miller, H. N. Sather, and G. D. Hammond.** Children's Hospital National Medical Center, Washington, DC

1039 Pediatric Phase I Trial of Carboplatin: A Childrens Cancer Study Group Report. **P. S. Gaynon, L. J. Ettinger, D. Moel, S. E. Siegel, E. S. Baum, W. Krivit, and G. D. Hammond.** Childrens Cancer Study Group

1043 Pharmacokinetics of Continuous-Infusion High-Dose Thiotepa. **W. D. Henner, T. C. Shea, E. A. Furlong, M. D. Flaherty, J. P. Eder, A. Elias, C. Begg, and K. Antman.** Dana-Farber Cancer Institute, Boston, Massachusetts

1049 Carboplatin or Iproplatin in Advanced Non-Small Cell Lung Cancer: A Cancer and Leukemia Group B Study. **H. Kreisman, S. Ginsberg, K. J. Propert, F. Richards, S. Graziano, and M. Green.** Cancer and Leukemia Group B

1053 Selective Treatment of Metastatic Lymph Nodes With Combination of Local Hyperthermia and Temperature-Sensitive Liposomes Containing Bleomycin. **S. Maekawa, K. Sugimachi, and M. Kitamura.** Kyushu University, Fukuoka, Japan

1061 Treatment Evaluation in Active Control Studies. **T. R. Fleming.** University of Washington, Seattle

1067 Inadequacy of Predicted Creatinine Clearance as Guide to Chemotherapy. **D. F. McDermott, A. Galindo, R. L. Sherman, E. A. Jaffe, and M. W. Pasmantier.** Cornell University Medical College, New York, New York

1071 Management of Learned Food Aversions in Cancer Patients Receiving Chemotherapy. **R. D. Mattes, C. Arnold, and M. Boraas.** Monell Chemical Senses Center, Philadelphia, Pennsylvania

REVIEW ARTICLE

1079 How Large Should a Phase II Trial of a New Drug Be? **R. Simon.** National Cancer Institute, Bethesda, Maryland

BRIEF REPORTS

1087 Chemotherapy of Adult Soft Tissue Sarcoma With Combination of Doxorubicin and Methotrexate. **P. Presgrave, R. L. Woods, M. H. Tattersall, A. S. Coates, J. A. Levi, R. M. Fox, and D. Hedley.** Royal North Shore Hospital, St. Leonards, Sydney, New South Wales, Australia

1089 Inhibitory Action of Flurbiprofen and Mopidamole on Tumor Lung Metastasis Formation in Mice. **A. Mamyt-**

beková, K. Řežábek, J. Grimová, and J. Svobodová. Research Institute for Pharmacy and Biochemistry, Prague, Czechoslovakia

1091 Oral Gestrinone: A Novel Antiprogestin With No Antitumor Activity in Endocrine-Sensitive Breast Cancer. **D. Cunningham, J.-C. Gazet, H. T. Ford, and R. C. Coombes.** St. George's Hospital, London, England

1093 Facilitation of Emergence of Multidrug-Resistant State by Alteration of Tumor Environment: Implications From Competitive Ecology Models. **S. Michelson.** Rhode Island Hospital and Brown University, Providence

CLINICAL TRIALS SUMMARIES

1095 Phase II Trial of Diaziquone in Patients With Refractory and Relapsing Multiple Myeloma: A Southwest Oncology Group Study. **W. J. Stuckey, J. Crowley, L. H. Baker, N. R. Larrimer, K. H. Hanson, J. D. Bonnet, and L. A. White, Jr.** Southwest Oncology Group

1097 Phase II Study of Isotretinoin in the Treatment of Advanced Non-Small Cell Lung Cancer. **S. M. Grunberg and L. M. Itri.** University of Southern California Comprehensive Cancer Center and Los Angeles County-University of Southern California Medical Center

1099 Phase II Study of Caracemide in Advanced or Recurrent Non-Small Cell Lung Cancer. **C. P. Belani, M. Eisenberger, D. Van Echo, D. Hiponia, and J. Aisner.** University of Maryland Cancer Center and Baltimore Veteran's Administration Medical Center

1101 Phase II Trial of Bisantrene in Hepatocellular Carcinoma: A Southwest Oncology Group Study. **T. D. Brown, T. R. Fleming, R. A. Shildt, and J. D. Cowan.** Southwest Oncology Group

1103 Phase II Trial of Ifosfamide/Mesna in Metastatic Adult Renal Carcinoma. **A. De Forges, J. P. Droz, M. Ghosn, and C. Theodore.** Institut Gustave-Roussy, Villejuif, France

1105 Phase II Study of Spirohydantoin Mustard for the Treatment of Recurrent Malignant Gliomas. **M. Prados, L. Rodriguez, M. Seager, P. Silver, and V. Levin.** University of California, San Francisco

1107 Phase II Trial of Prednimustine as First-Line Chemotherapy in Patients With Advanced Breast Cancer. **E. M. Rankin, C. Harvey, R. K. Knight, and R. D. Rubens.** Imperial Cancer Research Fund, Guy's Hospital, London, England

1109 Phase II Study of Mitoxantrone in Untreated and Previously Minimally Treated Patients With Metastatic Soft Tissue Sarcomas. **I. Quirt, E. Eisenhauer, V. Bramwell, M. Knowling, C. Grafton, W. Hirte, M. Cripps, and A. Maksymiuk.** National Institute of Canada Clinical Trials Group

1111 Phase II Study of Fludarabine Phosphate in Previously Untreated Patients With Hepatoma: A Southwest Oncology Group Study. **W. H. Harvey, T. R. Fleming, G. Beltran, J. H. Saiers, N. Oishi, and D. D. Von Hoff.** Southwest Oncology Group

1113 Continuous-Infusion Amsacrine in Patients With Refractory Acute Myelogenous Leukemia. **E. H. Estey, M. J. Keating, K. B. McCredie, and E. J. Freireich.** The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston

1115 Ifosfamide Plus 5-Fluorouracil for Treatment of Adenocarcinoma of the Pancreas. **P. J. Loehrer, Sr, S. D. Williams, and C. R. Nichols.** Indiana University Medical Center, Indianapolis

1117 Phase II Study of Deoxydoxorubicin in Patients With Advanced Liver Cancer. **D. J. Perry, D. A. Van Echo, and R. Mick.** Cancer and Leukemia Group B

1119 Oral Urea in Treatment of Liver Metastases From Colorectal Adenocarcinoma. **L. Levin, W. Kocha, and A. Driedger.** London Regional Cancer Centre, Canada

LETTERS

1121 Continuous Sc Infusion of Metoclopramide for Treatment of Narcotic Bowel Syndrome. **E. Bruera, C. Brennels, M. Michaud, and N. MacDonald.** Cross Cancer Institute, Edmonton, Alberta, Canada

1122 Severe and Fatal Toxic Effects Observed in Treatment With High- and Low-Dose Leucovorin Plus 5-Fluorouracil for Colorectal Carcinoma. **J. L. Grem, D. D. Shoemaker, N. J. Petrelli, and H. O. Douglass, Jr.** National Cancer Institute, Bethesda, Maryland

1123 Carboplatin, Etoposide, and Bleomycin for Treatment of Stage IIC Seminoma Complicated by Acute Renal Failure. **M. Farhangi and S. H. Weinstein.** University of Missouri, Columbia

1124 Ifosfamide/Mesna and Hematuria. **C. B. Pratt and M. P. Goren.** St. Jude Children's Research Hospital, Memphis, Tennessee

1125 Generation of Dose Intensity-Response Data Suggested for Drug Studies. **W. M. Hryniuk.** Hamilton Regional Cancer Centre, Ontario, Canada

1127 ANNOUNCEMENTS

Dacarbazine, Vindesine, and Cisplatin Combination Chemotherapy in Advanced Malignant Melanoma: A Phase II Study[1]

Stein Gundersen[2,*]

Both cisplatin (CDDP) and vindesine (a new vinca alkaloid derivative) have proven to have antitumor activity against melanoma cell lines and in early clinical trials among patients with advanced malignant melanoma (1–4). Synergistic activity of cisplatin and vindesine together has been demonstrated in non-small cell lung cancer (5). In a European Organization for Research and Treatment of Cancer phase II study a response rate of 30% was reported by combining CDDP and vindesine among patients with advanced malignant melanoma (6). This is higher than that reported in most large series with CDDP and vindesine used as single agents.

Dacarbazine (DTIC) has been considered the most active single-agent treatment, with response rates reported between 10% and 20% (7). At our institution the response rate among > 200 patients was found to be 14% (unpublished data).

Thus, it seemed logical to evaluate a three-drug combination of DTIC, CDDP, and vindesine (CiViDiC) among patients with advanced malignant melanoma.

MATERIALS AND METHODS

Criteria for entry in the study included: (*a*) histologically proven diagnosis of malignant melanoma and recurrent or metastatic disease not amenable to curative surgery and/or radiotherapy; (*b*) measurable or evaluable lesions with documented progression within 2 months prior to entry in this study; (*c*) performance status ≤ 2 according to the World Health Organization (WHO) scale; (*d*) life expectancy ≥ 3 months; (*e*) ≤ 75 years of age; and (*f*) no prior irradiation to measurable or evaluable disease. CNS involvement excluded patients from the study. A total of at least two courses were given, unless this was clearly not in the best interest of the patient. The maximum number of courses was four.

Response criteria were used as follows: *complete response (CR)*—the disappearance of all known disease and no new lesions in other sites, determined by two observations not less than 4 weeks apart; *partial response (PR)*—a $\geq 50\%$ decrease of the sum of the product of the two longest measurements of measurable lesions, without appearance of any new lesions, lasting for at least 4 weeks; *stable disease*—a $< 50\%$ decrease of the sum of the product of the two longest measurements of all measurable lesions, lasting for at least 8 weeks; *progressive disease*—a $\geq 25\%$ increase in the size of at least one measurable or evaluable lesion, or the appearance of new lesions; and *early death*—death during the first 4 weeks without severe toxicity.

The duration of response was determined from the start of treatment until the documentation of disease progression. Survival was determined from the start of treatment.

The treatment outline of CiViDiC is shown in table 1. Therapy cycles were repeated on Day 21. In case of significant hematologic toxicity prior to a planned course, treatment was postponed to Day 28. Weekly blood cell counts were undertaken.

RESULTS

Thirty patients with advanced malignant melanoma were entered in the study. Three patients died within 4 weeks after start of treatment and were considered early deaths and not evaluable with regard to response. Patient characteristics are shown in table 2. There were 17 males and ten females. Thirteen patients were previously treated with chemotherapy. One patient had been treated with triglycidylurazol, one with lomustine, one with vinblastine, and the rest with azolastone. All previous treatment had been given for metastatic disease. All patients had been without treatment for at least 6 weeks. None of the previously treated patients had responded to the therapy. Table 3 shows the number of courses received by the patients.

One patient had soft tissue metastases only, while 26 had visceral metastases with or without soft tissue metastases. Of the 27 patients evaluable for response, 20 were also fully evaluable for toxicity.

[1] Received Aug 20, 1986; revised June 29, 1987; accepted July 17, 1987.

[2] Department of Medical Oncology and Radiotherapy, The Norwegian Radium Hospital, Montebello, Oslo, Norway.

*Reprint requests to: Stein Gundersen, MD, Department of Medical Oncology and Radiotherapy, The Norwegian Radium Hospital, Montebello, Oslo 3, Norway.

TABLE 1.—Treatment outline of CiViDiC in advanced malignant melanoma*

Drug	Dose (mg/m^2)	Day
Cisplatin	100	1
Vindesine	3	1
DTIC	250	1-5

*Courses were repeated every 3 wks.

Response data are shown in table 4, which lists responses according to sex, localization of metastases, and previous treatment. Altogether, there were 12 responses among 27 patients (44%): four achieved CR (15%) and eight achieved PR (30%). The four CRs were in patients with lung metastases only. Five responses (two CRs and three PRs) were seen among the previously treated patients, and seven (two CRs and five PRs) were seen among the patients who had had no previous treatment.

The durations of CR were 2+, 4+, 4, and 6 months, with two patients still in CR 2 and 4 months after treatment was started. The median duration of PR was 4 months (range, 2-6).

There were 18 responses among 37 patients (49%) with lung and soft tissue metastases versus only two responses among 11 patients (18%) with liver metastases.

All patients experienced considerable nausea and vomiting, usually WHO grade 2 on Day 1, and then less pronounced nausea during the days that only DTIC was given. Median wbc count nadir was 2.2×10^9/L (range, 1.1-5.8) and median platelet count nadir was 123×10^9/L (range, 28-355). The increase in creatinine level was 12 μmols/L (range, 0-22). Clinical signs of infection, bleeding, ototoxicity, or renal failure were not seen.

DISCUSSION

CiViDiC appeared to have significant activity against advanced malignant melanoma with 12 CRs and PRs among 27 patients (44%, with 95% confidence limits of 25%-63%) (8). In particular, lung and soft tissue metastases responded well, while less activity was seen for liver metastases. Although this is not a randomized study and the number of patients was limited, the observed number of responses clearly exceeded that expected for single-agent therapy, although re-evaluation will be required in subsequent phase III trials. Patients who had previously received chemotherapy also responded.

Other groups have utilized similar regimens with somewhat varying results. Kleeberg et al (9) reported a response rate of about 25%, but the dose of cisplatin was half of the dose reported in this study. Carey et al (10) reported a response rate of 24% by combining vinblastine and DTIC with cisplatin; also in this study the dose of cisplatin was half of the dose in the present study. Retsas and Nicoll (11) gave cisplatin, vinblastine, and vindesine with and without bleomycin alternating with DTIC and vincristine and reported 30 responses among 64 patients with lung, lymph node, and soft tissue disease.

In this study a higher response rate than that experienced with vindesine and DTIC was reported in lung and soft tissue. The precise role of cisplatin is at present being analyzed through a multicenter randomized study, where vindesine and DTIC are compared to the same combination plus cisplatin.

The main toxic effect was gastrointestinal intolerance, although in some cases nausea and vomiting were somewhat subdued with high-dose metoclopramide. Bone marrow depression was seen regularly, but myelosuppression did not require dose-schedule modifications at

TABLE 3.—Courses

No. of courses	No. of patients
1	5
2	12
3	4
4	6

TABLE 2.—Patient characteristics

Characteristic	No. of patients
Total	30
Early death	3
Evaluable for response	27
Sex	
Male	17
Female	10
Previous chemotherapy	13
No previous chemotherapy	14
Site of metastases	
Soft tissue only	1
Visceral ± soft tissue	26
Median age in yrs (range): 55 (29-71)	

TABLE 4.—Response*

		Response			
Parameter	Total	CR	PR	Stable disease	Disease progression
Total	27	4	8	5	10
Male	17	2	5	4	6
Female	10	2	3	1	4
Visceral metastases	26	3	8	4	10
Lung	20	4	6	3	7
Liver	11	0	2	5	4
Soft tissue metastases	17	2	6	2	8
Previous treatment	13	2	3	3	5
No previous treatment	14	2	5	2	5

*Values = No. of patients.

any course. Slight increases in creatinine values were seen but were not of clinical significance in this trial. Alopecia was regularly seen when two or more courses had been given.

Despite the high primary sensitivity, most patients eventually relapsed. The impact on survival is unclear and can only be answered through phase III studies. Therefore, in advanced disease, clinical trials aimed at identifying new active compounds still should have high priority.

REFERENCES

1. BECHER R, and SCHMIDT CG. Ergebnisse der Chemotherapie des malignen Melanoms mit *cis*-Platinum II. *In* Cisplatin: Derzeitiger Stand und Neue Entwicklungen in der Chemotherapie Maligner Neoplasien (Seeber S, Schmidt CG, Nagel GA, et al, eds). Basel, S. Karger, 1980, pp 103–111.
2. OSIEKA R. Die präklinische Entwicklung von *cis*-platin (*cis*-diamino-dichloroplatin II). *In* Cisplatin: Derzeitiger Stand und Neue Entwicklungen in der Chemotherapie Maligner Neoplasien (Seeber, S, Schmidt CG, Nagel GA, et al, eds). Basel, S. Karger, 1980, pp 1–122.
3. RETSAS S, PEAT I, ASHFORD R, ET AL. Updated results of vindesine as a single agent in the therapy of advanced malignant melanoma. Cancer Treat Rev 7:(suppl)87–90, 1980.
4. VOIGT H, MEIGEL WN, MEISSNER K, ET AL. Erfahrungen mit det hochdosierten *cis*-Platin-Therapie beim metastasierten malignen Melanom. Onkologie 5:120–129, 1982.
5. CASPER ES, GRALLA RJ, and GOLBEY RB. Vindesine (DVA) and *cis*-dichlorodiammineplatinum(II) (DDP) combination chemotherapy in non-small cell lung cancer (NSCLC). Proc Am Assoc Cancer Res and ASCO 20:337, 1979.
6. DODION P, CZARNETZKI BM, MULDER JH, ET AL. Cisplatin and vindesine combination chemotherapy in advanced malignant melanoma. Proc ASCO (1)185:c-719, 1982.
7. MULDER JH, DODION P, CAVALLI F, ET AL. Cisplatin and vindesine combination chemotherapy in advanced malignant melanoma: an EORTC phase II study. Eur J Cancer Clin Oncol 18:1297–1301, 1982.
8. POCOCK S. Confidence limits for percentages. *In* Clinical Trials. New York, Wiley and Sons, 1983.
9. KLEEBERG UR, MULDER J, RÜMKE P, ET AL. EORTC-Malignant Melanoma Cooperative Group (MMCG). *In* Proceedings of the First International Conference on Melanoma, Venice, May 6–9, 1985, Abstr 152.
10. CAREY RW, GREEN MR, and ANDERSON J. Vinblastine-dimethyltriazenoimidazole carboxamide (DTIC)—cis-platinum (VDP): active regimen in metastatic melanoma. Proc ASCO 2:237, 1983.
11. RETSAS S, and NICOLL J. Effective cyclic combination chemotherapy in advanced metastatic malignant melanoma (MMM), using cisplatin (CP), vinblastine (VLB), vindesine (VDS), with and without bleomycine (BL), alternating with DTIC (DC) and vincristine (VCN). The (B) DOV 3 regime. Proc ASCO C-998, 1984.

Continuous 5-Day Infusion of Vinblastine for Percutaneous Hepatic Arterial Chemotherapy for Metastatic Breast Cancer[1]

Giuseppe Fraschini,[2,*] Gary Fleishman,[3] Chusilp Charnsangavej,[2] C. Humberto Carrasco,[2] and Gabriel N. Hortobagyi[2,4]

We assessed the therapeutic efficacy and toxicity of continuous hepatic infusion of vinblastine in the treatment of breast cancer predominantly metastatic to the liver. Twenty-six patients previously treated with one or more chemotherapeutic regimens received vinblastine at a dose of 2.0 mg/m^2 daily for 5 days, via percutaneously inserted intra-arterial catheters, at 3–4-week intervals. Nine of 25 evaluable patients (36%) achieved partial response and four (16%) had minor response. For responding patients, the median time to disease progression was 21 weeks (range, 12–99), with a median survival of 11 months (range, 4–29) from the beginning of hepatic arterial infusion. The toxicity of the treatment was acceptable, and drug-related effects were comparable to those seen in patients with breast cancer treated by iv continuous infusion of vinblastine at slightly lower doses. We observed two episodes of transient inappropriate antidiuretic hormone secretion. Percutaneous hepatic arterial infusion of vinblastine had significant activity in the treatment of breast cancer metastatic to the liver. [Cancer Treat Rep 71:1001–1005, 1987]

In our experience, vinblastine given as a 5-day continuous iv infusion has significant activity in patients with metastatic breast cancer (1,2). Other investigators have reported a lower degree of activity (3) or none (4,5) in small patient groups treated with somewhat lower doses.

The results of clinical trials suggested that this agent has a steep dose-response effect (2). In clinical pharmacologic studies, vinblastine displayed rapid plasma clearance (6,7) and significant hepatic extraction (6). Theoretically, these are the characteristics of agents suitable for intra-arterial hepatic infusion chemotherapy (8). Because vinblastine has these two properties, hepatic arterial delivery could allow the use of higher total doses, thereby increasing the tumor exposure to the drug without increasing the drug's systemic concentration and relative toxicity. Increased local exposure to an agent such as vinblastine with dose-dependent effect should heighten its antineoplastic activity.

Supported by these theoretical considerations, we proposed to assess the clinical efficacy and toxicity of vinblastine delivered as a continuous hepatic arterial infusion (HAI) in treating patients with breast cancer metastatic to the liver and refractory to chemotherapy.

PATIENTS AND METHODS

Selection of Patients

Between May 1979 and June 1985, 26 patients who had breast cancer predominantly metastatic to the liver received HAI of vinblastine in accordance with a prospectively designed protocol. Eligibility criteria for this program were previous treatment with at least one chemotherapy regimen, Zubrod performance score (9) of 0–3, life expectancy $\geq$ 12 weeks, and adequate bone marrow reserve, which was defined as an absolute granulocyte count $>$ 2000/mm^3 and a platelet count $>$ 100,000/mm^3.

After signing an informed consent form approved by the institutional review board, the patients were registered for the treatment protocol with the institutional central data management office.

Pretreatment Characteristics

Pretreatment evaluation included complete history and physical examination, complete blood and platelet counts, hepatic and renal function tests, a serum CEA test, and hepatic evaluation by imaging techniques.

[1] Received Apr 3, 1987; revised June 29, 1987; accepted July 17, 1987.

[2] Departments of Medical Oncology (*G. Fraschini* and *G. N. Hortobagyi*) and Radiology (*C. Charnsangavej* and *C. H. Carrasco*), The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston.

[3] Hematology-Oncology Associates of Houston, TX.

[4] We thank Theresa Criswell for her secretarial assistance in preparing the manuscript.

* *Reprint requests to:* Giuseppe Fraschini, MD, Department of Medical Oncology, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, 1515 Holcombe Blvd, Houston, TX 77030.

TABLE 1.—Pretreatment characteristics of 25 evaluable patients*

Characteristic	
Age (yrs)	
Median	51
Range	30–73
Disease-free interval (mos)	
Median	14
Range	0–91
Menopausal status	
Premenopausal	12
Postmenopausal	13
Zubrod performance score	
Median	1
Range	0–3
Duration of prior therapy (mos)	
Median	12
Range	2–44
No. of prior regimens	
Median	1
Range	1–5
No. of metastatic sites	
Liver only	14
Liver and others	11

*Unless otherwise specified, values = No. of patients.

The pretreatment characteristics of the 25 evaluable patients are shown in table 1. With the exception of one patient who had relapsed while receiving adjuvant combination chemotherapy that did not contain doxorubicin, all patients had received doxorubicin. One patient had received vinblastine HAI in the attempt to consolidate a good partial response (PR) induced by front-line systemic chemotherapy, and five patients had received only adjuvant chemotherapeutic combinations. The other patients had been refractory to one or more chemotherapeutic regimens. Four patients were refractory to continuous iv infusion of vinblastine, and four had received prior HAI chemotherapy with either cisplatin (three) or mitomycin and floxuridine (one).

Eleven patients had extrahepatic metastases that were small or quite stable; these involved the bone in five patients, bone and pleura in one patient, the brain in two who had responded to radiotherapy, and the lung in one. In addition, two patients had undergone surgical resection of chest wall recurrence.

Treatment

All patients were admitted to the hospital for the angiographic procedures and therapy. Percutaneous infusion catheters were positioned into the proper or common hepatic artery following insertion by the Seldinger technique (10). When multiple hepatic arteries were found, the minor vessels were occluded with Gelfoam or stainless-steel coils to redistribute flow through the major vessel and intrahepatic collateral vessels (11).

After the catheter was placed, the patients received a continuous intra-arterial infusion of vinblastine at a starting dose of 2.0 mg/m^2 daily for 5 days. Each daily dose was dissolved in 1 L of 5% dextrose in water; about 15,000 units of sodium heparin were added, and the solution was delivered by a volumetric infusion pump that assured a steady flow rate. The heparin concentration was adjusted to maintain a partial thromboplastin time of about 1.5–2 times the upper normal values, to minimize the risks of thromboembolic complications related to the presence of a catheter in arterial vessels (12). The correct position of the infusion catheters was assessed by abdominal radiographs daily and fluoroscopically whenever catheter displacement was suspected (12). Radioisotope flow studies to assess correct catheter placement and extrahepatic flow were done in a minority of the patients when the studies became available in our institute.

The starting dose of vinblastine was reduced by 20% in patients who had tolerated only substandard doses of systemic chemotherapy or had abnormal liver function (bilirubin $>$ 2.0 mg/dl). Additionally, the doses were adjusted in subsequent courses to obtain granulocyte count nadirs of 500–1000/mm^3 in the absence of other significant toxic reactions.

The treatments were generally repeated at 3-week intervals, although longer intervals became necessary in some patients. The wbc and platelet counts were repeated weekly. Hepatic and renal functions, CEA, and tumor measurements by imaging techniques were assessed before each course.

Treatment Response

Response to therapy was assessed by physical examination and imaging techniques including radionuclide scan, sonography, computerized tomography (CT), and hepatic angiography. In addition, when applicable, the response seen by imaging techniques was correlated with CEA serum concentrations. A PR was defined as a $>$ 50% decrease in the sum of the products of the two major perpendicular diameters of all lesions visible in the imaging test. When the metastatic disease appeared to diffusely infiltrate the liver and produced no nodular lesion that could be measured by imaging techniques, the degree of liver involvement was estimated by CT and angiography as the percentage of liver replacement by the tumor. In these patients, PR was defined as a $\geq$ 50% decrease in the percentage of replacement, with concurrent reduction of liver size and improvement in CEA concentrations and liver function test results, when applicable. Minor response (MR) was defined as a $<$ 50% reduction in tumor size in accordance with the criteria described here. No change was defined as no objective change in evaluable disease for $\geq$ 8 weeks. Progressive disease was defined as any objective increase in tumor measurement or any new lesion. All responses were assessed based on the consensus of a panel of three or more experienced radiologists and oncologists.

TABLE 2.—Results of continuous 5-day infusion of vinblastine

	No. of patients
Treated	26
Not evaluable	1
Evaluable	25
Partial response	9 (36%)
Minor response	4 (16%)
No change	5 (20%)
Progressive disease	7 (28%)

RESULTS

One of 26 patients entered was lost to follow-up after the first course of therapy and was not evaluable for response or toxicity.

The 25 evaluable patients received a median of three courses of vinblastine intra-arterially (range, one to five). The results are shown in table 2. The 95% confidence interval for the response rate observed was 18%–57%. Seven responding patients had nodular lesions that were measurable by imaging tests. The remaining two responding patients had angiographic and CT evidence of diffuse liver replacement by metastases, which appeared to decrease much more than 50%, with concomitant reduction of liver size and improvement of liver function, CEA concentrations, and performance status.

Median time to disease progression was 21 weeks (range, 12–99) for patients with PR; > 12 weeks (range, 8+ to 30) for patients with MR; and 12 weeks (range, 8+ to 14) for patients who experienced no change. Median survival was 11 months (range, 4–29) for patients with PR; 11 months (range, 10–19) for patients with MR; and 4 months (range, 2 wks to 14 mos) for nonresponding patients.

Responses were seen in poor-risk patients with high tumor burden, multiple previous therapies, and poor performance. Two patients with PR attained significant improvement of performance scores and palliation of symptoms.

TOXICITY

The toxic effects observed during 65 courses given to the 25 evaluable patients are listed in table 3. Myelosuppression was moderate, and the patients generally found the other toxic reactions tolerable. Average initial and final daily doses were 1.92 and 1.96 mg/m^2, respectively.

Catheter displacement was documented 13 times (in eight patients) and required repositioning by the radiologist. In five instances, the displacement was discovered by routine daily abdominal x-ray examination, and the patients affected had not complained of any significant related symptoms. In the remaining eight instances, the patients complained of nausea or emesis and abdominal pain, which were attributed to gastroduodenitis. Gastrointestinal (GI) symptoms were usually mild and resolved within a few days, and no GI bleeding occurred. Consequently, no barium studies or endoscopy was considered necessary to better define GI toxicity.

One patient who had a percutaneous catheter inserted via the brachial artery developed a thrombosis of this vessel, which was lysed successfully by local fibrinolytic therapy. Constipation was a frequent complaint, although the patients received prophylactic therapy with mild laxatives. Frank paralytic ileus occurred in two patients who also had severe myelosuppression. Of the three patients who experienced sepsis with leukopenia, two responded to antibiotic therapy. The third patient, who had a history of pyelonephritis and diabetes mellitus, died of acute renal failure, which probably started as acute tubular necrosis induced by the contrast dye used for the angiogram and was complicated by myelosuppression and sepsis. This patient was considered as having died from toxic effects.

Two patients developed a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) within 1 week of the institution of HAI infusion. Diagnosis was based on evidence of severe hyponatremia with normal renal function and no clinical evidence of volume depletion. Serum osmolality was abnormally low and was paired with disproportionately high urine osmolality

TABLE 3.—Toxic effects in 25 evaluable patients*

Toxic effect	
Hematologic (cells/mm^3)	
Absolute granulocyte count nadir	
Median	1020
Range	0–6400
Platelet count nadir	
Median	213,000
Range	41,000–415,000
Catheter-related	
Catheter displacement	8 (32)
Mild bleeding at insertion site	6 (24)
Hepatic arterial aneurysm	1 (4)
Brachial arterial occlusion	1 (4)
Drug-related	
Mild nausea/emesis	10 (40)
Gastroduodenitis	8 (32)
Constipation	8 (32)
Paralytic ileus	2 (8)
Stomatitis	1 (4)
Fever during infusion	8 (32)
Fever with leukopenia	6 (24)
Sepsis	3 (12)
Weakness/fatigue	2 (8)
Myalgia	1 (4)
Anorexia	1 (4)
Chemical hepatitis	1 (4)
Inappropriate ADH secretion	2 (8)
Hyponatremia	1 (4)
Hepatic arterial occlusion	7 (28)
Hepatic arterial narrowing	2 (8)
Death from toxic effects	1 (4)

*Unless otherwise specified, values = No. of patients (%). ADH = antidiuretic hormone.

and urine sodium concentration much higher than 20 mEq/L. In addition, both patients experienced severe myelosuppression for 1 week, with transient complete agranulocytosis.

The SIADH syndrome responded to standard therapy with fluid restriction, infusion of small quantities of hypertonic saline solution, and oral demeclocycline. In one patient, hyponatremia resolved in 1 week, and two additional courses of therapy at reduced doses caused no significant electrolyte abnormality. The second patient, who was affected by prolonged paralytic ileus, recovered from hyponatremia after 2 weeks, but because of these severe complications, she refused further therapy and was considered to have had treatment failure caused by toxicity.

Complete occlusion of the hepatic arteries was often preceded by diffuse, progressive narrowing of the hepatic arterial circulation attributed to vinblastine-induced arteritis. This complication prevented further intra-arterial therapy in two patients with PR, three with MR, and one with no change, who were then maintained on continuous iv vinblastine infusion.

Three patients whose hepatic lesions responded to treatment had measurable extrahepatic metastases; these involved the bone in two patients and the brain in one. No responses were observed at these sites.

DISCUSSION

Although 6 years elapsed between accrual of the first and the last patient in this study, the patients were treated in accordance with the same written protocol and treatment was comparable. As a possible exception, we noted a lower incidence of catheter-related complications in the more recent years, which may be explained by the increased experience of our angiologists and the availability of radioisotope flow studies.

Vinblastine given as a 5-day continuous iv infusion has produced objective remission in > 30% of patients with refractory metastatic breast cancer (1,2), although response was documented for only 13% of the hepatic metastases (2). In the present study, vinblastine given intra-arterially produced responses in > 30% of the patients with hepatic metastases. The durations of response and survival observed are impressive when we consider that the responding patients received a median of only three courses of intra-arterial therapy. Their better outcome may, however, reflect the more benign nature of their disease. Responses occurred also in patients with adverse prognostic characteristics or in those who had been unresponsive to HAI with other agents; in some patients, performance status and symptoms clearly improved.

Myelosuppression and other toxic reactions encountered in our study were comparable to those observed when vinblastine was given iv at lower dosages to patients with breast cancer (2). Pharmacology studies to support the theoretical advantage of HAI delivery were not performed in our patients, and comparison of the toxic effects and responses seen in this study with those noted with the lower dosages of vinblastine given iv may not be reliable because the patient populations were dissimilar. The efficacy and comparatively limited toxic effects seen in our patients and the observation of two responses in patients refractory to vinblastine given iv suggest, however, that some hepatic extraction of the drug occurred and that intra-arterial delivery improved its therapeutic index.

The treatment was generally well tolerated at the doses used, although the incidence of nausea and emesis was higher than expected from systemic drug toxicity. These symptoms were often a manifestation of mild gastroduodenitis induced by extrahepatic flow of the intra-arterial vinblastine infusion.

Hepatic arterial narrowing and occlusion secondary to the sclerosing activity of vinblastine was a major cause of treatment discontinuation. This problem may have limited the intensity and duration of response in the affected patients, who could only receive systemic infusion at lower doses. Arguably, the hypoxemia induced by arterial occlusion may have contributed, by a mechanism similar to therapeutic embolization, to the responses seen (13), but our data do not support this theory. Seven of nine patients who attained PR did not develop arterial occlusion, and evidence of arterial occlusion or marked narrowing followed the documentation of tumor regression in the other two.

An unusual toxic effect was SIADH. This toxicity has been documented for vinca alkaloids, especially vincristine (14,15) and only occasionally for vinblastine, with the suggestion that the occurrence depends on dose amplitude (16–18). In our series, both patients who experienced SIADH had severe leukopenia, and one had a prolonged ileus, which infers that these patients were unusually sensitive to vinblastine. When the first patient was re-challenged with vinblastine HAI at lower doses, the SIADH did not recur. This confirmed that SIADH is a dose-dependent complication and suggested that the affected patients may continue a chemotherapy trial after appropriate dosage adjustment.

In summary, HAI of vinblastine appeared to be an effective palliative treatment for breast cancer metastatic to the liver and was acceptable to most patients. This agent may be useful in combination with other effective intra-arterial chemotherapeutic agents that have no significant overlapping toxicity.

REFERENCES

1. YAP H-Y, BLUMENSCHEIN GR, KEATING MJ, ET AL. Vinblastine given as a continuous 5-day infusion in the treatment of refractory advanced breast cancer. Cancer Treat Rep 64:279–283, 1980.
2. FRASCHINI G, YAP H-Y, HORTOBAGYI GN, ET AL. Five-day continuous infusion vinblastine in the treatment of breast cancer. Cancer 56:225–229, 1985.

3. SHAH MK, CREECH RH, CATALANO RB, ET AL. Phase II study of vinblastine infusion in the treatment of refractory advanced breast cancer. Proc ASCO 1:73, 1982.
4. TANNOCK I, ERLICHMAN C, PERRAULT D, ET AL. Failure of 5-day vinblastine infusion in the treatment of patients with advanced refractory breast cancer. Cancer Treat Rep 66:1783–1784, 1982.
5. INGLE JN, AHMANN DL, GERSTNER JG, ET AL. Evaluation of vinblastine administered by 5-day continuous infusion in women with advanced breast cancer. Cancer Treat Rep 68:803–804, 1984.
6. OWELLEN RJ, and HARTKE CA. The pharmacokinetics of 4-acetyl-tritium vinblastine in two patients. Cancer Res 35:975–980, 1975.
7. LU K, YAP H-Y, and LOO TL. Clinical pharmacokinetics of vinblastine by continuous intravenous infusion. Cancer Res 43:1405–1408, 1983.
8. CHEN H-SG, and GROSS JF. Intra-arterial infusion of anticancer drugs: theoretic aspects of drug delivery and review of responses. Cancer Treat Rep 64:31–40, 1980.
9. ZUBROD CG, SCHNEIDERMAN M, FREI E, ET AL. Appraisal of methods for the study of chemotherapy of cancer in man: comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. J Chronic Dis 11:7–33, 1960.
10. SELDINGER SI. Catheter replacement of the needle in percutaneous arteriography: a new technique. Acta Radiol 39:368–376, 1953.
11. CHUANG VP, and WALLACE S. Hepatic arterial redistribution for intraarterial infusion of hepatic neoplasms. Radiology 135:295–299, 1980.
12. CHUANG VP, and WALLACE S. Arterial infusion and occlusion in cancer patients. Semin Roentgenol 16:13–25, 1981.
13. CHUANG VP, and WALLACE S. Hepatic artery embolization in the treatment of hepatic neoplasms. Radiology 140:51–58, 1980.
14. SLATER LM, WAINER RA, and SERPICK AA. Vincristine neurotoxicity with hyponatremia. Cancer 23:122–125, 1969.
15. CUTTING HO. Inappropriate secretion of antidiuretic hormone secondary to vincristine therapy. Am J Med 51:269–271, 1971.
16. GINSBERG SJ, COMIS RL, and FITZPATRICK AV. Letter: Vinblastine and inappropriate ADH secretion. N Engl J Med 296:941, 1977.
17. ANTONY A, ROBINSON WA, ROY C, ET AL. Inappropriate antidiuretic hormone secretion after high dose vinblastine. J Urol 123:783–784, 1980.
18. RAVIKUMAR TS, and GRAGE TB. The syndrome of inappropriate ADH secretion secondary to vinblastine-bleomycin therapy. J Surg Oncol 24:242–245, 1983.

Randomized, Double-Blind, Cross-Over Study Comparing Prochlorperazine and Lorazepam With High-Dose Metoclopramide and Lorazepam for the Control of Emesis in Patients Receiving Cytotoxic Chemotherapy[1,2]

James F. Bishop,* Max Wolf, Jane P. Matthews, Karen Scott, Stephen Ackland, Kally Yuen, Carmel Morton, Brian L. Hillcoat, and Ian A. Cooper[3]

To further define optimal combinations of antiemetics, high-dose metoclopramide and lorazepam (M+L) were compared with prochlorperazine and lorazepam (P+L) in a randomized, double-blind, cross-over study. Both patient and observer assessments were documented in 66 patients receiving cisplatin and noncisplatin chemotherapy. M+L significantly reduced the severity of vomiting ($P = 0.01$), duration of vomiting ($P = 0.05$), and number of vomiting episodes ($P = 0.003$). Comparing the severity or duration of nausea, M+L and P+L were not significantly different. M+L significantly reduced severity of vomiting ($P = 0.005$) and number of vomiting episodes ($P = 0.03$) in the cisplatin subset. The number of vomiting episodes was also reduced in the noncisplatin subset ($P = 0.03$). When asked to nominate a preferred regimen, 41% of patients preferred P+L, 35% preferred M+L, and 24% rated them equally. M+L was associated with significantly more anxiety and less sedation than P+L. Patient assessments produced similar results to observer assessments but gave a broader understanding of our patients' tolerance to chemotherapy. M+L is a superior regimen in controlling vomiting induced by chemotherapy. [Cancer Treat Rep 71:1007-1011, 1987]

Nausea and vomiting remains a most distressing side effect for patients receiving cytotoxic chemotherapy. Recently, an increasing number of clinical studies have combined antiemetics, including lorazepam, prochlorperazine, dexamethasone, and high-dose metoclopramide, with encouraging results (1-3). However, the search for more effective antiemetic combinations continues.

In a randomized study, high-dose metoclopramide was reported to be significantly superior to prochlorperazine in objectively reducing the number of vomiting episodes and the volume of emesis (4). Other studies have also confirmed the value of high-dose metoclopramide (5-8). However, only patients receiving cisplatin chemotherapy were assessed. The value of high-dose metoclopramide in non-cisplatin-containing chemotherapy remains unclear. In most antiemetic studies, only observer assessments are recorded. The patients' assessment of high-dose metoclopramide regimens is unknown.

We have previously reported the superior antiemetic efficacy of prochlorperazine and lorazepam (P+L) when compared to prochlorperazine and placebo in a randomized, double-blind study (3). In that study, P+L was a highly effective combination which significantly reduced the severity and duration of nausea, the severity of vomiting, and the number of vomiting episodes compared to prochlorperazine plus placebo. In this study, we have compared P+L with high-dose metoclopramide and lorazepam (M+L). This study design allows us to study a new combination (M+L) and to make some comparisons of prochlorperazine and high-dose metoclopramide in the presence of lorazepam.

PATIENTS AND METHODS

Patients

All adult cancer patients who were to receive two consecutive chemotherapy courses likely to induce significant nausea and vomiting were eligible. The cytotoxic drugs received included cisplatin alone or in combination, doxorubicin, daunorubicin, mechlorethamine, dactinomycin, cyclophosphamide, dacarbazine, and mitomycin. Patients with a past history of mental illness or prior adverse reactions to benzodiazepines, prochlor-

[1] Received Mar 24, 1986; revised June 25, 1987; accepted July 22, 1987.
[2] Supported in part by Wyeth Pharmaceuticals Pty, Ltd, Australia.
[3] Peter MacCallum Cancer Institute, Melbourne, Australia.

* *Reprint requests to:* James F. Bishop, MD, Department of Cancer Medicine, Peter MacCallum Cancer Institute, 481 Little Lonsdale St, Melbourne 3000, Australia.

perazine, or metoclopramide were ineligible. Patients with significant respiratory disorders were excluded. Patients without prior chemotherapy were preferred.

Study Design

The study was designed to compare the antiemetic effects of M+L and P+L in two consecutive chemotherapy courses in each patient. The study was a randomized, double-blind, cross-over study. All patients received lorazepam for both study courses. Patients were randomized to M+L or P+L for the first study course and crossed over to the alternate regimen for the second course. The iv flasks containing metoclopramide or prochlorperazine were indistinguishable except by a code number recorded in the pharmacy.

Dose

All patients received lorazepam [0.05 mg/kg orally (taken to the nearest 1 mg)] 30 minutes prior to chemotherapy and again 7.5 hours after chemotherapy. This dose of lorazepam was shown in our previous study to produce significant antiemetic effects. Metoclopramide (2 mg/kg in 50 ml of normal saline) was infused iv over 15 minutes. Metoclopramide was given 30 minutes before chemotherapy and again at 1.5, 3.5, and 7.5 hours after chemotherapy. The metoclopramide schedule was modified from Gralla et al (4). Prochlorperazine (12.5 mg in 50 ml of normal saline) was infused iv over 15 minutes. Prochlorperazine was given 30 minutes before chemotherapy and again at 3.5 and 7.5 hours after chemotherapy. A placebo infusion of 50 ml of normal saline was given at 1.5 hours after chemotherapy to patients receiving prochlorperazine. The prochlorperazine schedule was chosen to conveniently double-blind the study.

Assessment of Study Parameters

At 24 hours following each chemotherapy course, patients completed a questionnaire which assessed the severity of vomiting; duration of vomiting; number of vomiting episodes; severity of nausea; duration of nausea; degrees of anxiety, sedation, and tolerance; extrapyramidal side effects; hallucinations; diarrhea; and course preference. Patients graded the severity of vomiting, nausea, anxiety, and sedation as none, mild, moderate, severe, or very severe. The degree of tolerance was recorded as very well, well, not too badly, poorly, or very poorly. Durations of nausea and vomiting were recorded to the nearest hour and the number of vomiting episodes was noted. The nurses caring for the patient were asked to make a similar assessment over 24 hours for all parameters with the exception of severity and duration of nausea, patient tolerance, and course preference. Extrapyramidal side effects, hallucinations, and diarrhea were specifically listed on the patient assessment form. In addition, nurses were asked to record motor restlessness, tremor, oculogyric crises, convulsions, or diarrhea after consultation with a medical officer. Thus, both patient and observer assessments were documented independently. Nurses caring for the patients were a small constant group involved with this study. Cumulative data such as the number of vomiting episodes were updated as nursing shifts changed. For other data the worst experience observed was the one noted on the final data base.

Statistical Methods

The main comparisons of M+L and P+L have been made using the Wilcoxon signed-rank test for paired data. The natural data have been used where numerical answers were given, such as number of vomiting episodes, or scores from 1 to 5 for graded data, such as none, mild, moderate, severe, and very severe. P values given refer to two-tailed tests.

Carry-over effects were tested for, as described by Koch (9), by comparing the sum of results in Courses 1 and 2 for the two randomization arms using the Wilcoxon rank-sum test. There was no indication of carry-over effects in any of the parameters studied ($P > 0.1$ for all parameters). In the absence of such carry-over effects treatment effects were estimated (10), and the significance of such effects was tested by using the Wilcoxon rank-sum test comparing the difference in results between courses for the two randomization arms (9). Similarly, period effects were estimated by comparing differences in the P+L and M+L courses for the two arms. Thus, tests for differences in effect of treatment are valid whether or not period effects are present. Patient treatment preferences were compared using the above methods by creating a variable with the values −1 if Course 1 was preferred, 0 if there were no course preferences, and +1 if Course 2 was preferred. Similarly, course preferences were compared by creating a variable with the values −1 if M+L was preferred, 0 if there were no treatment preferences, and +1 if P+L was preferred.

To facilitate interpretation of the data, summary statistics based on observed differences between the pairs of courses for each patient have been given.

The incidence of extrapyramidal side effects, hallucinations, and diarrhea in the two treatment arms was compared using Fisher's exact test.

The magnitude of treatment differences which could be detected with probability (power) 0.9 using two-tailed tests at significance level 0.05 were estimated retrospectively for each parameter, based on the estimated variances. For graded data (eg, severity of nausea, severity of vomiting, and anxiety) the required differences all lay between 0.3 and 0.5, where a value of 0.3 corresponds to an average of 30% of patients experiencing a lower grade on one particular arm compared with the other arm. For patient preferences, the expected percentage of patients preferring one treatment arm needed to be 40% greater (in absolute value) than the percentage preferring the other arm to be detected with power 0.9.

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Eligible	66
Sex	
Male	27
Female	39
No prior chemotherapy	39
Prior chemotherapy	27
Median age in yrs (range): 55 (20–73)	
Diagnosis	
Breast cancer	15
Lymphoma	12
Bladder cancer	11
Small cell lung cancer	8
Head and neck cancer	5
Ovarian cancer	5
Others	10

RESULTS

Sixty-six patients received two consecutive courses of the same cytotoxic chemotherapy and were eligible for analysis (table 1). Thirty patients received P+L first and 36 received M+L first. Thirty-one patients (47%) received platinum-containing regimens and 35 (53%) received non-platinum-containing combinations.

Fifty-five patients received the identical dose of chemotherapy for the two courses analyzed and an additional 11 had minor dose adjustments of < 20% between Courses 1 and 2. The treatment effects were estimated and tested separately in the 55 patients who received identical doses and in the 11 patients with dose adjustments. In addition, the effects were compared between the two groups using a t test. There were no significant differences for any parameter relating to nausea and vomiting and in every case the differences were of the same sign in the two groups. The results quoted below, therefore, refer to all 66 patients.

In all 66 evaluable patients, the antiemetics were delivered as defined in the protocol. Fourteen additional patients have been excluded from the analysis because they received only one course of antiemetics. Twelve of these patients had their chemotherapy stopped (nine patients) or substantially altered (three) after Course 1. Two patients were withdrawn because of unacceptable sedation (P+L, one patient; M+L, one).

Using patient assessments, M+L was associated with significantly less severe vomiting compared to P+L ($P = 0.01$; tables 2 and 3). Vomiting was assessed as none in 39% of M+L courses compared with 24% of P+L courses (table 3). The severity of vomiting was also significantly reduced with M+L in patients receiving cisplatin chemotherapy ($P = 0.005$) but not in patients receiving noncisplatin chemotherapy ($P = 0.4$). The clinical benefit of these results in the cisplatin subset was obvious, with no vomiting in 39% of M+L courses and in only 16% of P+L courses. For patients receiving noncisplatin chemotherapy, 41% had no vomiting with M+L and 32% had no vomiting with P+L.

The number of vomiting episodes was significantly less with M+L ($P = 0.003$), with a median of two episodes for M+L courses and three episodes for P+L courses. The number of vomiting episodes was significantly less for M+L courses in patients receiving noncisplatin chemotherapy ($P = 0.03$). M+L also significantly reduced the duration of vomiting ($P = 0.05$). The median duration of vomiting was 2 hours for M+L courses and 4 hours for P+L courses.

Comparison of other parameters assessed by patients failed to reveal any further statistically significant advantage for the M+L regimen. These parameters included severity of nausea, duration of nausea, sedation, and overall tolerance to treatment.

Patients documented that anxiety was significantly more severe while receiving M+L ($P = 0.01$), particularly for patients who received cisplatin ($P = 0.005$). Overall, no anxiety was recorded by 61% of patients during M+L courses compared with 76% during P+L.

When asked to nominate a preferred antiemetic regimen, 24% rated them equally, 35% preferred M+L courses, and 41% preferred P+L courses ($P = 0.67$). The reasons patients gave for this preference were based on nausea and vomiting experienced (82%), anxiety (9%), or degree of sedation (9%).

TABLE 2.—Comparison of patient assessments of M+L vs P+L*

Parameter	M+L superior	P+L superior	M+L and P+L equal	*P* value†
Severity of vomiting	37	14	49	0.01‡
Duration of vomiting	47	23	30	0.05‡
No. of vomiting episodes	50	26	24	0.003‡
Severity of nausea	34	20	46	0.13
Duration of nausea	41	34	25	0.7
Anxiety	11	28	61	0.01‡
Tolerance	30	37	33	0.3
Preferred regimen	35	41	24	0.6

*Unless otherwise specified, values = % of patients.

†Based on the Wilcoxon signed-rank test for paired data. Summary results only are quoted in this table.

‡*P* values ≤ 0.05.

TABLE 3.—Patient assessments of severity of vomiting: direct comparison of all M+L and P+L courses

	Severity in P+L courses						
	None	Mild	Moderate	Severe	Very severe	Unknown	Total for M+L courses
Severity in M+L courses							
None	14	8	4	0	0	0	26 (39%)
Mild	2	14	4	4	0	0	24 (36%)
Moderate	0	1	4	4	0	0	9 (14%)
Severe	0	2	3	0	0	1	6 (9%)
Very severe	0	0	0	1	0	0	1 (2%)
Total for P+L courses	16 (24%)	25 (38%)	15 (23%)	9 (14%)	0	1	66

The results obtained independently by nursing staff paralleled the results reported by patients above. The severity of vomiting was highly significantly less with M+L for all patients ($P = 0.009$) and for those receiving cisplatin ($P = 0.02$) (table 4). For patients receiving cisplatin, 45% receiving M+L were observed to have no vomiting compared with 23% receiving P+L. For patients receiving noncisplatin chemotherapy, no vomiting was observed in 46% receiving M+L compared with 37% receiving P+L. The number of vomiting episodes was significantly less for all patients ($P = 0.003$) and also cisplatin patients during M+L courses ($P = 0.02$). Overall, the duration of vomiting tended to be less during M+L courses ($P = 0.07$). In contrast to patient assessments, nursing staff did not detect any differences in anxiety associated with the two antiemetic regimens. Sedation caused by the two regimens was not significantly different as graded by patients ($P = 0.08$). However, when graded by nurses, significantly more sedation was observed during P+L courses ($P = 0.05$).

Other toxic effects experienced were not significantly different when the regimens were compared. Extrapyramidal symptoms, as assessed by nurses and patients, were equivalent and occurred in 9% of M+L and 3% of P+L courses ($P = 0.3$). Diarrhea was seen in 30% of M+L courses and 20% of P+L courses ($P = 0.2$). Hallucinations occurred in 8% of M+L courses and 2% of P+L ($P = 0.2$).

The comparison of the antiemetic effects of M+L and P+L was similar whether assessed by nurses or patients. In addition, nurse and patient assessments have been formally compared. Patient and nurse assessments of severity of vomiting were identical in 58% and identical or within one category in 91%, with the nurse ratings > 1 category more severe than those of patients in 2% and the patient ratings > 1 category more severe than the nurses in 7%.

All major parameters were tested for period effects, that is, differences between the results in Courses 1 and 2 which could not be attributed to treatment differences. Vomiting tended to be more severe for the second course, with an increase in the number of vomiting episodes and a significantly increased duration of vomiting ($P = 0.03$). Patients tolerated the first course better than the second course ($P = 0.009$). These period effects do not invalidate the comparison of treatments, however, because of the chosen methods of comparison.

Thirty-nine (59%) of the patients had received no prior chemotherapy at study entry. Treatment and period effects were estimated separately for patients with or without prior chemotherapy. No significant differences were found between these two groups of patients.

DISCUSSION

Lorazepam is a minor tranquilizer of the benzodiazepine group. It relieves free-floating and somatic anxiety, has hypnotic effects, and produces amnesia (11). In comparison to diazepam, lorazepam has a slower onset of action but a longer duration (12). These properties suggested that lorazepam may be a useful adjunct to antiemetic therapy for patients receiving cytotoxic chemotherapy. In a randomized, double-blind, placebo-

TABLE 4.—Observer assessments comparing M+L vs P+L*

Parameter	M+L superior	P+L superior	M+L and P+L equal	P value†
Severity of vomiting	39	17	44	0.009‡
Duration of vomiting	44	26	30	0.07
No. of vomiting episodes	48	17	35	0.003‡
Anxiety	23	27	50	0.7

*Unless otherwise specified, values = % of patients.

†Based on the Wilcoxon signed-rank test for paired data. Summary results only are quoted in this table.

‡P values < 0.05.

controlled study, lorazepam significantly added to the antiemetic effect of prochlorperazine (3). The combination of lorazepam and dexamethasone was superior to high-dose metoclopramide alone in controlling vomiting (1). In this study, we have compared our previously demonstrated best antiemetic combination, P+L with M+L.

High-dose metoclopramide alone was previously reported to reduce the number of vomiting episodes and the volume of emesis when compared to prochlorperazine in patients receiving cisplatin (4). Carr et al (6) have reported that prochlorperazine and high-dose metoclopramide have equal efficacy when measuring the number of vomiting episodes in a randomized parallel design. Our study demonstrates the value of the combination M+L in reducing the severity, duration, and number of vomiting episodes. M+L significantly reduced the severity of vomiting in patients receiving cisplatin chemotherapy and the number of vomiting episodes in patients receiving other chemotherapy. Thus, M+L is a superior regimen in the control of vomiting.

The use of parameters assessed by the patient has allowed us to assess patient course preference. Using paired comparisons, only 35% of all patients preferred M+L courses, 41% preferred P+L, while 24% rated them equal. In addition, only 35% of cisplatin-treated patients preferred M+L courses. Since the intent of antiemetic therapy is to improve the patient's tolerance to chemotherapy, patient course preference may be an important parameter. Eighty-two percent of patients stated that they based their choice of antiemetic regimen on their experience of nausea and vomiting. However, despite significantly better control of vomiting, most patients did not choose M+L. The reason for this discrepancy is unclear. Patient tolerance to chemotherapy may be related to severity and duration of nausea but not vomiting, since the two regimens were not significantly different in the control of nausea. If so, patient assessments may be important in evaluating antiemetics since nausea cannot be an observed parameter.

When using lorazepam, we have been concerned that patient assessments may be less accurate than observer assessments because of patient amnesia (13). In this study we collected both patient and observer assessments in parallel, analyzed treatment comparisons using both data sets, and formally compared the two. Comparisons of the antiemetic efficacy of the two regimens were similar using nurse or patient assessments. Formal comparison of the nurse and patient assessments revealed a high level of agreement for vomiting. However, in contrast to the patient assessments, anxiety was not noted to be increased with M+L using the nurse assessments. It is likely that the patient assessment of anxiety is more accurate. Observed sedation was significantly increased during P+L therapy but not noted to be different by patients. We assume that sedation may be more accurately assessed by an observer.

Sedation in patients receiving chemotherapy could be considered a desired action of an antiemetic or a side effect. When asked, patients varied as to the desirability of this effect. The higher degree of anxiety detected by patients during M+L courses would appear to suggest an advantage for P+L, especially in patients with preexisting anxiety and in whom vomiting is not severe. The incidence of extrapyramidal syndromes and other side effects was acceptably low and similar when the antiemetic regimens were compared.

This study extends our previous experience with P+L and we conclude that both M+L and P+L are highly effective. Since M+L significantly reduced the severity of vomiting, the duration of vomiting, and the number of vomiting episodes compared with P+L, M+L is clearly the preferred regimen if vomiting is distressing, especially in patients receiving cisplatin.

REFERENCES

1. GAGEN M, GOCHNOUR D, YOUNG D, ET AL. A randomized trial of metoclopramide and a combination of dexamethasone and lorazepam for prevention of chemotherapy induced vomiting. J Clin Oncol 2:696-701, 1984.
2. KRIS MG, GRALLA RJ, TYSON LB, ET AL. Improved control of cisplatin induced emesis with high-dose metoclopramide and with combinations of metoclopramide, dexamethasone and diphenhydramine. Cancer 55:527-534, 1985.
3. BISHOP J, OLVER IN, WOLF MM, ET AL. Lorazepam: a double blind, crossover study of a new antiemetic in patients receiving cytotoxic chemotherapy and prochlorperazine. J Clin Oncol 2: 691-695, 1984.
4. GRALLA RJ, ITRI LM, PISKO SE, ET AL. Antiemetic efficacy of high-dose metoclopramide: randomized trials with placebo and prochlorperazine in patients with chemotherapy induced nausea and vomiting. N Engl J Med 305:905-909, 1981.
5. FRYTAK S, MOERTEL CG, EAGAN RT, ET AL. A double blind comparison of metoclopramide and prochlorperazine as antiemetics for platinum therapy. Proc ASCO 22:421, 1981.
6. CARR B, BETRAND M, BROWNING S, ET AL. A comparison of the antiemetic efficacy of prochlorperazine and metoclopramide for the treatment of cisplatin-induced emesis: a prospective randomized, double-blind study. J Clin Oncol 3:1127-1132, 1985.
7. STRUM SB, MCDERMED JE, PILEGGI J, ET AL. Intravenous metoclopramide: prevention of chemotherapy induced nausea and vomiting. Cancer 53:1432-1439, 1984.
8. TYSON LB, CLARK RA, GRALLA RJ. High-dose metoclopramide: control of dacarbazine-induced emesis in a preliminary trial. Cancer Treat Rep 66:2108, 1982.
9. KOCH GG. The use of non-parametric methods in the statistical analysis of the two-period change over design. Biometrics 28: 577-584, 1972.
10. BROWN BW. The crossover experiment for clinical trials. Biometrics 36:69-79, 1980.
11. ELLIOT HW, NOMOF N, NAVARROG G, ET AL. Central nervous system and cardiovascular effects of lorazepam in man. Clin Pharmacol Ther 12:468-481, 1971.
12. DUNDEE JW, MCGOWEN AW, LILBURN JK, ET AL. Comparison of the actions of diazepam and lorazepam. Br J Anaesth 51:439-445, 1979.
13. LASZLO J, CLARK RA, HANSON DC, ET AL. Lorazepam in cancer patients treated with cisplatin: a drug having antiemetic, amnesic and anxiolytic effects. J Clin Oncol 3:864-869, 1985.

Preliminary Report on the Treatment of Esophageal Cancer by Intraluminal Microwave Hyperthermia and Chemotherapy[1]

Ding-Jiu Li* and Bing-Sen Hou[2]

Thirty-two cases of esophageal cancer were treated with thermochemotherapy from August 1984 to June 1985. A combination of bleomycin (20 mg per session iv) and cisplatin (0.5–0.9 mg/kg per session as low dose and 1.0–2.0 mg/kg per session as high dose), or of bleomycin, cisplatin (high dose), and cyclophosphamide (400–600 mg per session) were the treatment regimens. A 915-MHz microwave applicator was inserted into the lumen of the esophagus for heating. The temperature at normal adjacent tissue to the cancer was at 43–44°C, while the temperature of the cancer was at 45°C–50°C. Chemotherapy and hyperthermia were administered simultaneously, once a week for six to eight sessions. The response rate in the low-dose group was 36.4% (four of 11) and 81% (17 of 21) in the high-dose group. The complete response rate in the low-dose group was zero of 11 patients, with 38.1% (eight of 21) in the latter group. The relationship between power output and tumor response is also discussed. [Cancer Treat Rep 71:1013–1019, 1987]

Surgery and radiation therapy are the main treatment modalities for esophageal cancer. While a lot of patients are not good candidates for surgery or radiation therapy, chemotherapy could be of some use for them. However, the results of chemotherapy in esophageal cancer are far from ideal (1). During the past few years, we treated our patients with hyperthermia in combination with radiation therapy (2–4). It has been proved that the cytotoxicity of some antineoplastic drugs, such as bleomycin, doxorubicin, carmustine, cisplatin (DDP), etc, is much more effective at elevated temperature both in vitro and in vivo (5,6). However, very few clinicians have paid much attention to the possibility of improving their clinical results by combining drugs with hyperthermia so far, especially with local hyperthermia. Recently, from August 1984 to June 1985, we treated 32 cases of esophageal cancer with intraluminal microwave hyperthermia in combination with two or three antineoplastic agents.

MATERIALS AND METHODS

Patient Selection

The patients, ages 26–76 years old, were admitted to the hospital and diagnosed as squamous cell carcinoma proven by histology or cytology tests. The length of the lesion was 4–8 cm, which was within the effective heating zone. Among the 32 patients, only two cases recurred after radiation therapy.

Chemotherapy

Two drugs, bleomycin and DDP, and sometimes a third drug, cyclophosphamide, were used in combination in the regimen. All the patients received bleomycin, 20 mg per session iv. The dose of DDP was 0.5–0.95 mg/kg per session for the low-dose group (11 cases) and 1.0–2.0 mg/kg per session for the high-dose group (21 cases). In the latter group, 14 cases were also given cyclophosphamide, 400–600 mg per session.

Chemotherapy and hyperthermia were administered simultaneously, once a week for six to eight sessions. Hydration therapy, including infusion of hypertonic glucose, mannitol, and saline, was given on Days 1 and 2. In some cases antiemetics and sedatives were needed to control side effects.

Hyperthermia and Thermometry

A microwave set of WR-L-4 model with 915 MHz was used as the power. The intracavitary antenna designed and made in our laboratory was 120 mm in length, with a 90-mm effective heating zone measured in phantom (fig 1). The structure of the antenna and its thermodistribution are also shown in figure 1.

A thermocouple thermometry system modified from Chakraborty and Brezovich (7), and made in our laboratory with acceptable microwave interference and clinically acceptable accuracy, 0.2°C, was used for temperature measurement.

[1] Received Sept 17, 1986; revised July 17, 1987; accepted July 24, 1987.
[2] Department of Radiation Oncology, Henan Tumor Institute, Zhengzhou, Peoples Republic of China.

**Reprint requests to:* Ding-Jiu Li, MD, Department of Radiation Oncology, Henan Tumor Institute, Zhengzhou, Henan, Peoples Republic of China.

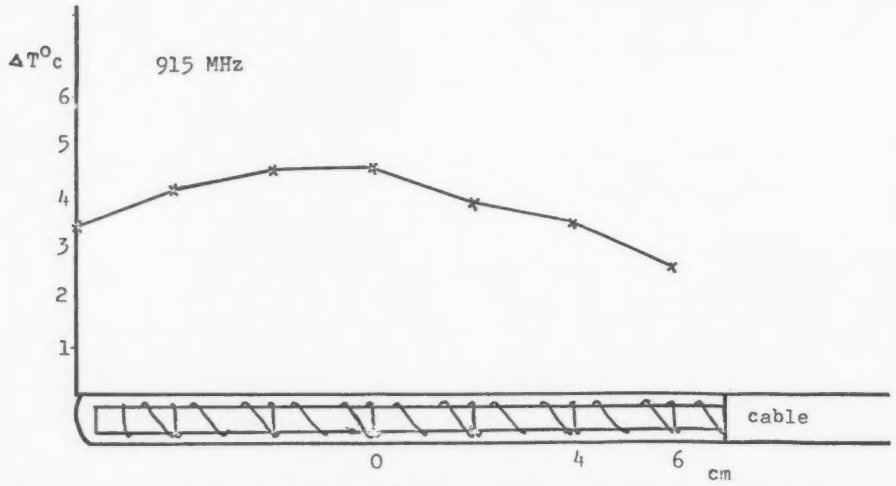

FIGURE 1.—The structure and the thermodistribution of the intracavitary radiator for the esophagus. The diameter is 5 mm. The effective heating area is about 100 mm in length. The antenna is the spiral structure connected with the outer conductor of the cable. The working frequency is 915 MHz. The temperature distribution at the surface of the antenna is measured in phantom. The thermocouples are located at the surface of the radiator and at the center (point 0) and 4 or 6 cm away from the center (point 4 or 6). Point 0 is in the center of the cancer and point 6 is measuring the temperature at the normal esophagus, whereas point 4 is measuring the temperature at the margin of the tumor or normal esophagus depending on the size of the tumor. During treatment, 3 temperature curves were plotted. Point 4 was the reference point and was kept at 43°C or 44°C.

Two or three thermocouples were located at the surface of the radiator to monitor the temperature at the middle of the tumor surface (point 0), the margin of the tumor (point 4), and the normal esophagus (point 6) as shown in figure 1. The thermocouple at the margin of the tumor (point 4 or 4 cm away from the center of the microwave field) served as the reference point. During heating, the temperature at the reference point was kept at 43°C or 44°C by regulating the power output. The heating time for each session was 60 minutes. A 1904-F trans-passing type power meter was for monitoring the power output and power reflected (fig 2).

Evaluation of the Treatment Result

The patients who received fewer than four treatment sessions were not included in this series. After five sessions, if the barium meal examination showed poor response, the patients were classified as no response and referred to other therapy. For those with some improvement, the whole course of treatment was carried through to the end.

Diagnostic criteria were evaluated by the barium esophageal gram. *Complete response* (CR) was defined as a tumor that is totally regressed with the esophageal wall smooth or slightly rigid during swallowing. *Partial response* (PR) was defined as any case that met the following criteria: (*a*) tumor regression > 50% in length; (*b*) if tumor had invaded the whole circle of the lumen, after treatment one side of the wall became smooth and

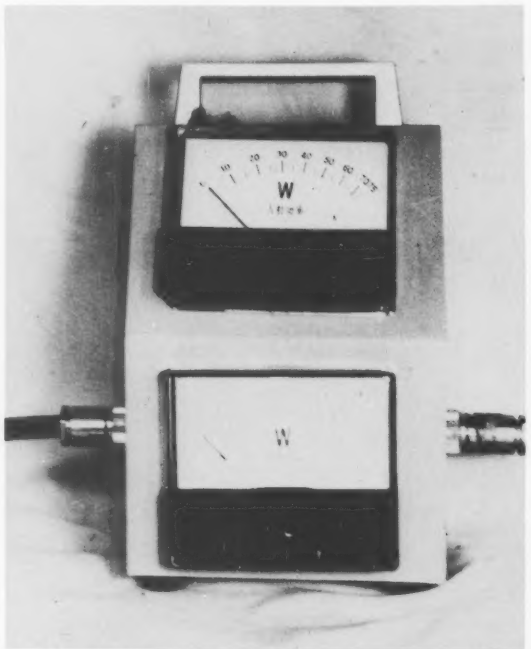

FIGURE 2.—1904-F trans-passing microwave power meter. Working frequency 200-1000 MHz. The upper meter is measuring the power output. The lower one is for power reflected.

TABLE 1.—Dose of drug and response rate

	Response [CR + PR (%)]	NR	Total	
Low dose	4 (36.4)	7	11	$P < 0.05$
High dose	17 (81)	4	21	
2 drugs	6 (85.7)	1		
3 drugs	11 (78.6)	3		
Total	21 (65.5)	11	32	

regular with the other side showing improvement; and (*c*) the lumen remained narrow but had no filling defect or grossly apparent smooth cavity. *No response* (NR) was defined as tumor regression < 50% in volume.

RESULTS

Response Rate and Dosage

The overall response rate (CR + PR) of the whole group was 65.5%; in the high-dose subgroup it was 81%. Among the high-dose group, no significant difference was seen between those treated under the two-drug regimen and those who received the three-drug regimen. As for the CR rate, it seemed that better results were obtained in the three-drug subgroup than in the two-drug subgroup (tables 1–3).

Length of Cancer and Response Rate

Under this heading, patients could be divided into other subgroups: (*a*) tumor length < 5 cm, and (*b*) tumor length > 5 cm. In either group no significant difference was found between their response rates (table 4).

Average Power Consumed and Tumor Response

The temperature at point 4 was kept at 43°C in a few early cases and 44°C for most cases during the course of treatment. By regulating the power output, the temperature at point 4 could be kept at the same level as the reference temperature. The power output and its reflection were recorded every minute. We used the same radiator for the same patient during the whole course of treatment. The radiator was put into the esophageal cavity. Therefore, we may consider: the power out (P_o) − power reflected (P_r) = power consumed (P_c); the P_c = power absorbed (P_a) by tissue; and P_a = P maintaining tissue temperature plus heat loss (blood flow conduction). If tissue temperature is kept unchanged at the reference temperature and heat loss through conduction is relatively unchanged, P_a would reflect the blood flow changes.

More power was needed to maintain the reference temperature at the same level during the course of treatment in the CR group (fig 3). Meanwhile, the $\overline{T}_a$ (average tumor temperature at point 0) was also going up, from 46.5 at the first session to 48°C at the sixth session. The P_c needed to maintain T_4 at the same level was gradually raised to 140% compared with the first session.

In the PR group, when the reference temperature was kept at the same level, the P_c was also rising during the course of treatment but $\overline{T}_a$ was not changed (fig 4). Figures 3 and 4 were of the same pattern.

In the NR group, when reference temperature and $\overline{T}_a$ were kept unchanged during the course of treatment, the P_c was not going up, but going down. This may be explained by the unchanged blood flow due to the remaining tumor mass (fig 5).

TABLE 2.—CR rates in different groups

	CR/total	(%)
Low dose		
Bleomycin + DDP	0/11	(0)
High dose		
Bleomycin + DDP	1/7	(14.3)
Bleomycin + DDP + cyclophosphamide	7/14	(50)

TABLE 3.—Response rate and length of tumor

	CR	PR	CR + PR (%)	NR	Total
< 5 cm	2	5	7 (58.3)	5	12
> 5 cm	6	8	14 (70)	6	20

Side Effects

The toxic effects of this regimen were not serious. The gastrointestinal side effects were loss of appetite, nausea, and vomiting. These occurred in 29 cases and lasted for 2–4 days. Leukopenia occurred in eight cases; two of them had a wbc count of 2000 and 2100/mm^3. Nonprotein nitrogen, urea nitrogen, and blood creatinine were all in the normal limits. Fever occurred at 1–3 hours after infusion in 12 cases and lasted for 2–4 hours; among them, three cases were at 40–41°C. Administration of antihistamine or antiemetics might prevent or minimize these side effects.

No serious side effects, such as perforation, hemorrhage, or esophageal burn, were seen during heating or as a result of passing the radiator into the esophagus in the total 198 treatment sessions. In one case the tumor temperature was > 50°C for 10 minutes; no side effect occurred.

TABLE 4.—Combination chemotherapy for esophageal carcinoma

Regimen*	Reference No.	Patients evaluable	Response rate (%)
DDP + bleomycin	1	61	15
DDP + bleomycin	1	17	24
DDP + DVA + bleomycin	1	68	53
DDP + adr + 5 Fu	1	21	33
DDP + VCR + bleomycin	10	32	47
DDP + bleomycin + heat	Present series	32	65.5

*DVA = vindesine; adr = doxorubicin; 5 Fu = 5 fluorouracil; VCR = vincristine; and heat = intraluminal microwave hyperthermia.

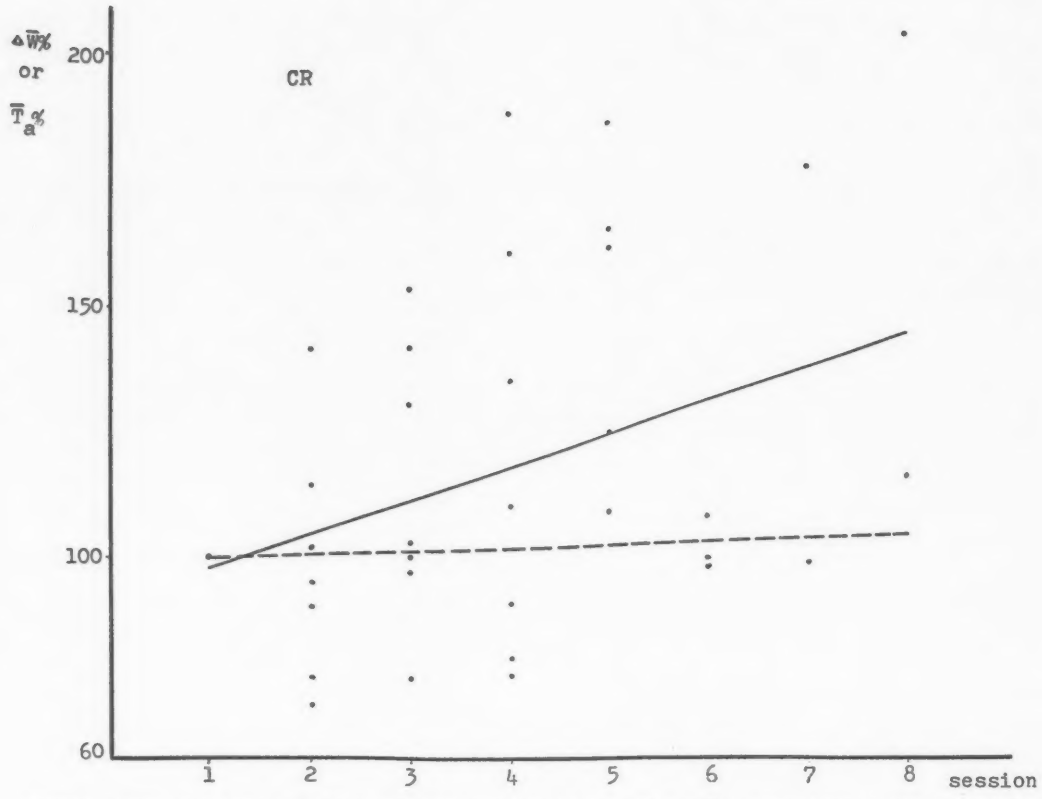

FIGURE 3.—Average P_c and average $\overline{T}_a$ in the course of treatment in the CR group. The P_c or $\overline{T}_a$ at first session was at 100%. T_4 was kept at 43°C or 44°C, which is not shown in this figure. The scattergram in this figure is the power in each case. The points of $\overline{T}_a$ are omitted. ..... indicates $\overline{T}_a$; —— indicates P_c.

Follow-up of the CR Patients

For the eight CR cases, all were followed > 1 year. Among them, two patients were living without evidence of recurrence, one of whom was followed for 26 months without recurrence. Two patients recurred and died at 12 and 14 months after treatment. The remaining four patients also recurred; one of them received surgery and three received radiation therapy.

Case Report

A 55-year-old male patient (Patient Y) had a squamous cell carcinoma at the middle segment of the esophagus. The tumor was 6 cm in length. He received cyclophosphamide, 0.6 g, bleomycin, 20 mg, and cisplatin, 100 mg per week, for 6 weeks. Hyperthermia: the temperature at the center of the esophagus was around 46°C, the reference temperature was 44°C, and the temperature of the normal esophagus (point 6) was about 42°C. Chemotherapy and hyperthermia were given simultaneously. The x-ray film showed a smooth and well-dilated esophageal cavity after treatment and 14 months afterward (figs 6 and 7).

DISCUSSION

The results of chemotherapy for esophageal cancer are far from ideal. The response rate of single-agent treatment was about 15%–20%, while that of the combination chemotherapy was 15%–50% (1). Several cases were reported with 5-year survival. Table 4 lists the results of some recent reports in chemotherapy for esophageal cancer.

From table 4, the response rate of this series is higher than that of others. The CR rate is 25% (eight of 32) for the whole group and 38.1% (eight of 21) for the high-dose cases. This high CR rate could not be explained by only the high drug dose. The synergistic effect of hyperthermia and drugs must have played an important role. It has been proved in vitro and in vivo (5) that the cytotoxicity of bleomycin, DDP, and cyclophosphamide is much increased at elevated temperature. However,

the ideal combination of heat and drugs remains to be investigated.

The esophageal cavity lies in a relatively stable state and is less influenced by the external environment. In the case of intracavitary hyperthermia, the microwave power (P_c) could be considered totally absorbed by the tumor and its nearby normal tissue. Some of the absorbed power was washed out by blood flow and conduction. The latter was usually less important than the former. The remaining absorbed power was for keeping the tissue temperature at an elevated level. During the course of treatment, the tumor mass was gradually replaced by the granulation tissue in the responsive cases. The blood flow in the granulation tissue was much higher than that in the cancer. During the process of tumor regression, the replacement of granulation tissue took place and led to the improvement of blood flow. In these cases, because more heat was washed out by the increased blood flow, more power was needed in order to maintain the reference temperature at the same level. In the nonresponsive cases, the tumor mass remained unchanged and no improvement of local blood flow happened. So, there was no need for more power to maintain the reference temperature (fig 5).

In experimental tumors, the tumor blood flow was usually lower than that of normal tissue and was without compensation during heating (8). Olch et al (9) pointed out that in some human cancer there was some functional adjustment during hyperthermia which might give some negative impact to the tumor regression. In our series, the average P_c was gradually going up in CR cases, while the P_c in NR patients was stable or had a slight downward trend. There might be some functional adjustment in the cancer tissue during hyperthermia in NR cases. From the above observation, we conclude that the P_c might be an indicator for tumor response during hyperthermia. And also, we may stress that there is a great need for research on human tumor blood flow during hyperthermia.

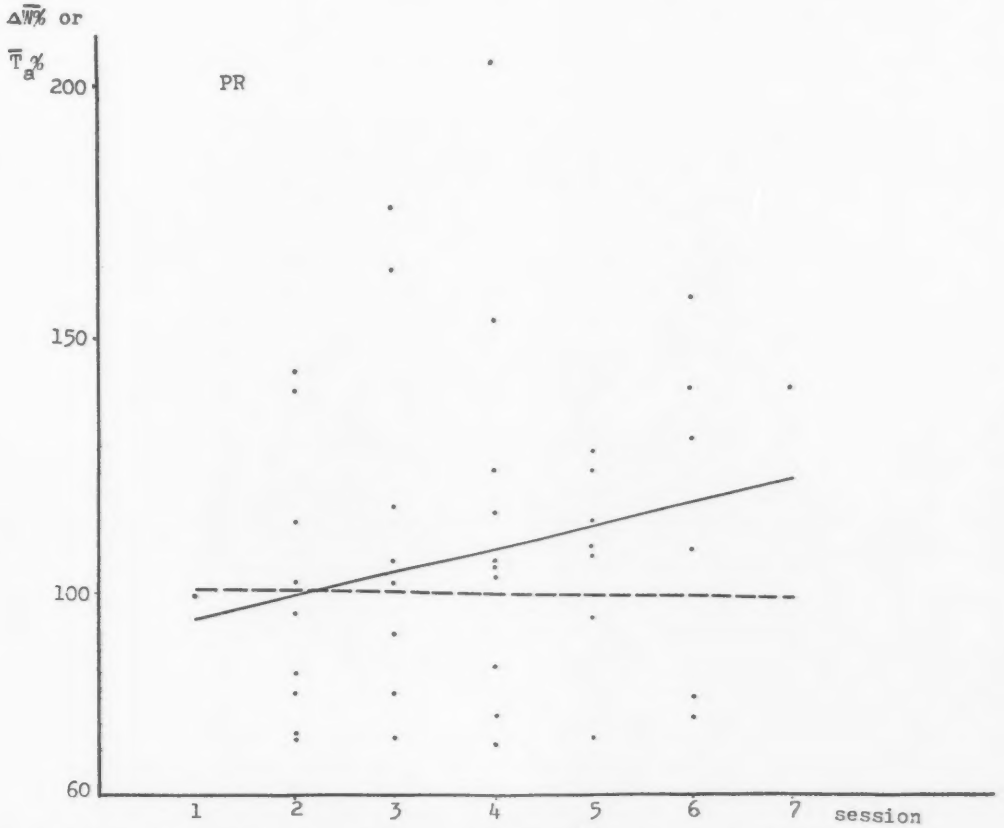

FIGURE 4.—Average P_c and average $\overline{T}_a$ in the course of treatment in PR cases. T_4 was kept at 43°C or 44°C and is not shown in the fig. ..... indicates $\overline{T}_a$; —— indicates P_c.

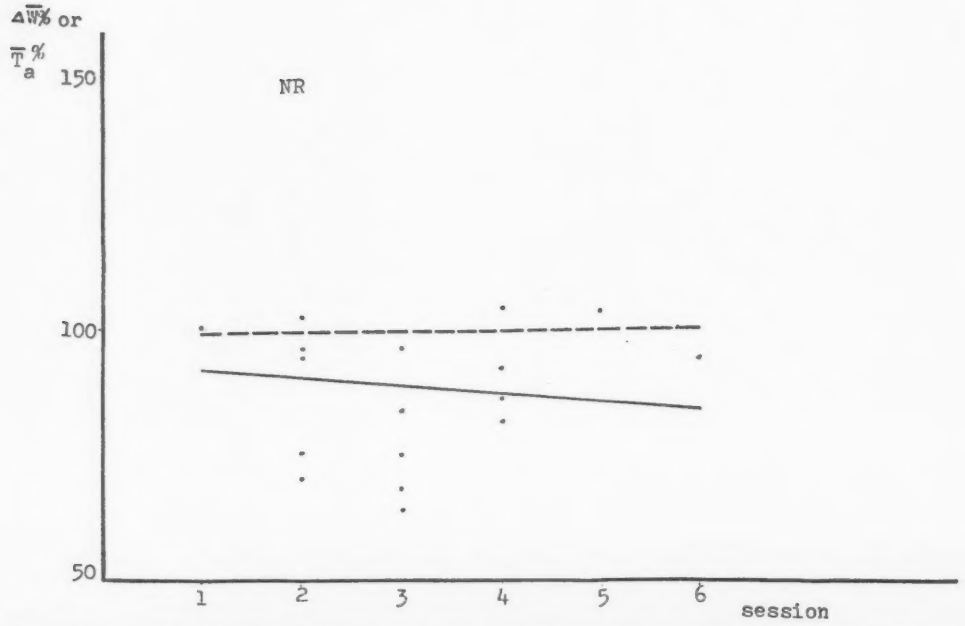

FIGURE 5.—Average P_c and average $\overline{T}_a$ in the course of treatment in NR cases. T_4 was kept at 43°C or 44°C and is not shown. ..... indicates $\overline{T}_a$; —— indicates P_c.

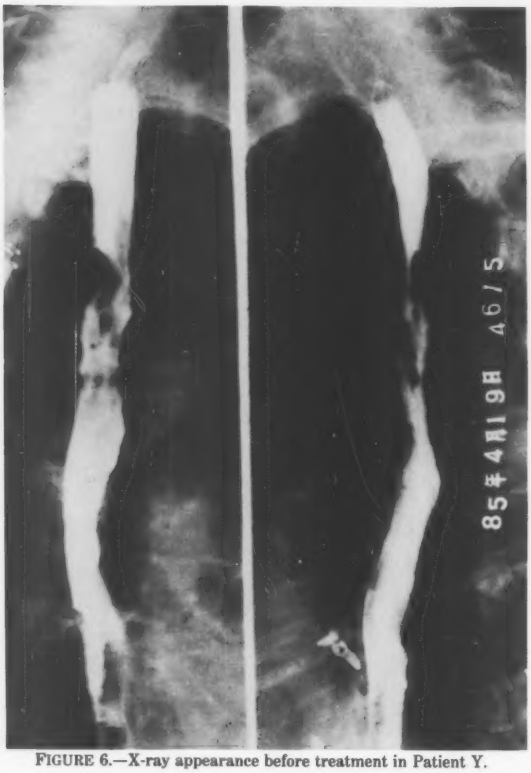

FIGURE 6.—X-ray appearance before treatment in Patient Y.

FIGURE 7.—X-ray appearance after treatment in Patient Y showing smooth and normal esophagus.

REFERENCES

1. KELSEN D. Chemotherapy of esophageal cancer. Semin Oncol 11:159–168, 1984.
2. LI DJ, WANG CQ, QUI SL, ET AL. Intraluminal microwave hyperthermia in the combined treatment of esophageal cancer: a preliminary report of 103 cases. Natl Cancer Inst Monogr 61:419–421, 1982.
3. SHA Y, LI DJ, QIU SL, ET AL. The combined treatment of esophageal cancer—a clinical pathological study of 42 cases. *In* Hyperthermic Oncology (Overgaard J, ed). London, Taylor & Francis, 1984, pp 371–374.
4. LI DJ. A randomized trial on the radiation combined with or without hyperthermia in the treatment of esophageal cancer. Cancer Res Prev Treat 13:187, 1986.
5. HAHN GM. Hyperthermia and Cancer. New York, Plenum Press, 1982.
6. HIRAMOTO RN, GHANTA VK, and LILLY MB. Reduction of tumor burden in a murine osteosarcoma following hyperthermia combined with cyclophosphamide. Cancer Res 44:1405–1408, 1984.
7. CHAKRABORTY DP, and BREZOVICH IA. Error sources affecting thermocouple thermometry in RF electromagnetic fields. J Microwave Power 17:17–28, 1982.
8. SONG CW. Effect of local hyperthermia in blood flow and microenvironment: a review. Cancer Res 44:4721s–4730s, 1984.
9. OLCH A, KAISER L, SIBERMAN A, ET AL. Blood flow in human tumors during hyperthermia therapy: demonstration of vasoregulation and an applicable physiological model. J Surg Oncol 23: 123–125, 1983.
10. WANG RL. The combination chemotherapy of DDP, bleomycin, and vincristine in esophageal cancer. Acta Acad Med Henan 19:58–59, 1984.

Comparison of the Actions of the Antiprogestin Mifepristone (RU486), the Progestin Megestrol Acetate, the LHRH Analog Buserelin, and Ovariectomy in Treatment of Rat Mammary Tumors[1,2,3]

G. H. Bakker,* B. Setyono-Han, M. S. Henkelman, F. H. de Jong, S. W. J. Lamberts, P. van der Schoot, and J. G. M. Klijn[4,5]

The effects of the synthetic antiprogestin mifepristone (RU486) on growth of dimethylbenzanthracene (DMBA)-induced mammary tumors in female rats were investigated. Prophylactic treatment with mifepristone (10 mg/kg/day) for 3 weeks starting from the day of first DMBA injection resulted in a doubling of the average tumor latency period (81 ± 16 days, $n = 17$ treated, versus 39 ± 5 days, $n = 75$ controls; $P < 0.005$) and was accompanied by a significant growth retardation as shown by lower body weight increments. A 3-week therapeutic treatment of rats bearing mammary tumors was performed by administration of different dosages of mifepristone (2.5, 10, or 40 mg/kg/day) or megestrol acetate (2.5 or 10 mg/kg/day), with the luteinizing hormone-releasing hormone agonist buserelin (40 μg/kg/day), buserelin plus mifepristone (10 mg/kg/day), or by ovariectomy. The effects of treatment on tumor load, pituitary, adrenal and reproductive organ weights, steroid receptor contents of mammary tumors, and blood plasma hormone concentrations were investigated. Mifepristone and megestrol acetate treatment gave rise to inhibition of mammary tumor growth with all dosages studied, in which mifepristone was more potent than megestrol acetate (80%-90% vs 40% inhibition, $P < 0.01$). In contrast, buserelin treatment and ovariectomy resulted not only in inhibition, but in tumor remission by about 50%. Combined treatment with buserelin and mifepristone gave the same tumor remission as resulted from ovariectomy or single treatment with buserelin. Estradiol-stimulated growth of the human mammary cancer MCF-7 cells in culture was fully abolished by mifepristone (3.6×10^{-8} M) or tamoxifen (4×10^{-8} M), whereas growth of MCF-7 cells under control incubation was not affected by either agent. Therefore, a direct inhibition of the growth of rat mammary tumor cells by mifepristone appears likely. Based on the effects of mifepristone on plasma hormone levels (increased: luteinizing hormone, estradiol, progesterone; unchanged: follicle-stimulating hormone, adrenocorticotropic hormone, corticosterone), organ weights (increased: pituitary, ovaries, uterus; unchanged: adrenals) and steroid receptor contents of mammary tumors (decreased: estrogen receptor and progesterone receptor contents), the main mechanism of action is probably a direct antiprogestational effect at the level of the mammary tumor cells through occupancy of the progesterone receptor. [Cancer Treat Rep 71:1021-1027, 1987]

The sensitivity of breast cancer cells to alterations in their hormonal environment by ablative or endocrine measures has been well documented (1-8). Current endocrine treatment of breast cancer patients involves administration of estrogens (2,3), antiandrogens (2,3), corticosteroids (9), aromatase inhibitors (10), and analogs of luteinizing hormone-releasing hormone (LHRH) (11,12), while antiestrogens (1-8,13,14) and high-dose

[1] Received Feb 11, 1987; revised July 14, 1987; accepted July 24, 1987.

[2] Supported in part by The Netherlands Cancer Foundation, grant RRTI 83-3. G. H. Bakker is the recipient of a legacy conferred upon The Dr. Daniel den Hoed Cancer Center by Mr. G. Nagel.

[3] Mifepristone was supplied by Dr. R. Deraedt, Roussel Uclaf, Romainville, France.

[4] Department of Endocrine Oncology (Biochemistry and Endocrinology) (*G. H. Bakker, B. Setyono-Han, M. S. Henkelman,* and *J. G. M. Klijn*), The Dr. Daniel den Hoed Cancer Center, Rotterdam, and the Departments of Biochemistry (*F. H. de Jong*), Clinical Endocrinology (*S. W. J. Lamberts*), and Endocrinology, Growth and Reproduction (*P. van der Schoot*), Medical Faculty, Erasmus University, Rotterdam, The Netherlands.

[5] We thank Dr. M. A. Blankenstein (Department of Clinical Endocrinology, State University, Utrecht, The Netherlands) for his initial contribution to the work described; L. Baggerman, H. Peters, H. Portengen, and P. Uitterlinden for their technical assistance, J. Marselje for preparation of the figures, and Mrs. A. Sugiarsi for preparation of the manuscript.

* *Reprint requests to:* G. H. Bakker, PhD, Department of Endocrine Oncology, The Dr. Daniel den Hoed Cancer Center, P. O. Box 5201, 3008 AE Rotterdam, The Netherlands.

progestins (7,14–16) are commonly used. In contrast to antiestrogens, treatment with high-dose progestins causes significant side effects mainly due to their corticosteroidal activity. New treatment modalities may involve using somatostatin analogs (17) or antiprogestins.

Recently, a steroid with antiprogestin activity (mifepristone, RU486) was developed (18,19). It was shown that mifepristone directly inhibits growth of human breast cancer cells in vitro after binding to the progesterone receptor (20). Extensive in vivo studies have been reported on treatment of hormone-dependent rat mammary tumors with the antiestrogen tamoxifen (21). With similar protocols as used in those tamoxifen studies, we have investigated the effects of chronic antiprogestin treatment on mammary tumor load, organ weights, plasma hormone concentrations, and tumor steroid receptor levels using the rat model of dimethylbenzanthracene (DMBA)-induced mammary tumors.

In the present study we also compared the effects of mifepristone with those of the progestin megestrol acetate, of ovariectomy, and of an LHRH analog (buserelin) on the growth of mammary tumors in rats.

MATERIALS AND METHODS

Female rats of the Sprague-Dawley strain were obtained from the Zentralinstitut fur Versuchstierzucht, Hannover, Federal Republic of Germany. Rats were kept four or five to a cage on wood shavings and received standard dry pellets (Hope Farms, Woerden, The Netherlands) and tap water ad libitum.

Tumor Induction

Dimethylbenzanthracene (DMBA, Fluka, Basel, Switzerland) was dissolved in olive oil at a concentration of 10 mg/ml by vigorous shaking. The solution obtained was stored in the dark. Induction of mammary tumors was performed with two intragastric administrations of 1 ml of DMBA solution given with a 1-week interval to 54–61-day-old rats (22).

Start of Treatments

Animals were weighed once a week and palpated twice weekly to detect the presence of mammary tumors. Treatment began when all rats (apart from those of the prophylactic mifepristone group) had palpable tumors (105–115 days of age). Rats were anesthetized with diethyl ether, and the size of the individual tumors was calculated from the product of the two largest perpendicular diameters measured with calipers. For each rat, the sum of the individual tumor areas represented the tumor load of the animal. Before treatment, rats were divided between control and treatment groups in such a way that the same average tumor load was obtained in each group.

Treatments

Prophylaxis.—A 3-week prophylactic treatment with mifepristone, provided by Dr. R. Deraedt, Roussel Uclaf, Romainville, France, was started the first day of DMBA injection by daily sc injection of the steroid (10 mg/kg/day) in 100 μl of olive oil, in two different experiments.

Therapy.—Therapeutic treatments were performed using groups of seven to nine rats (each weighing approximately 250 g) during 3 weeks, in six different experiments. Micronized mifepristone was suspended in olive oil at different concentrations which enabled daily sc administration of mifepristone in 100-μl injections. Megestrol acetate was purchased from Sigma, St. Louis, MO, and dissolved in olive oil. Buserelin was generously provided by Hoechst AG, Frankfurt am Main, Federal Republic of Germany. Buserelin work solution was made by dilution of the stock solution (1 mg/ml) with saline. Daily sc injections of megestrol acetate and buserelin were also administered in 100-μl solutions. Control animals received daily injections of 100 μl of saline.

The final dosages administered were: mifepristone, 2.5, 10, or 40 mg/kg/day, megestrol acetate, 2.5 or 10 mg/kg/day, and buserelin, 40 μg/kg/day. In the combined treatment with mifepristone (10 mg/kg/day) and buserelin, both solutions were administered at two distant loci on the back of the rat. Ovariectomy was performed by bilateral resection of the ovaries.

End of Treatments

After a 3-week treatment period, the tumor load was estimated again in anesthetized rats. Subsequently, rats were killed by decapitation. Blood was collected in heparinized tubes and plasma was stored at −20°C until assayed for luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), prolactin, estradiol, corticosterone, and progesterone. Tumor tissue was collected and stored at −70°C until assayed for estrogen and progesterone receptors. Finally, the weights of pituitary and adrenal glands, and of ovaries and uterus were recorded. Ovaries were fixed in Bouin's solution for histological analysis. They were embedded in paraffin wax and sectioned at 10 μm. Sections were mounted serially and stained with hematoxylin and eosin.

Steroid Receptor Assays

Estrogen receptors (ER) and progesterone receptors (PR) were assayed in homogenates of the mammary tumor tissue according to the European Organization for Research and Treatment of Cancer (EORTC) procedures (23) by multiple-point Scatchard analysis, using [2,3,6,7-^{3}H] estradiol (85–110 Ci/mmol) and [^{3}H]ORG-2058 (40–60 Ci/mmol) from Amersham International Plc, Bucks, England. Displaceable binding with a dissociation constant of < 4 nM was considered as specific binding to receptors.

Plasma Hormone Assays

Assay of LH and FSH was performed as described by Welschen et al (24). Estradiol was assayed with EIR-

kits obtained from EIR, Würenlingen, Switzerland. Progesterone was determined according to de Jong et al (25). Corticosterone was assayed using the antiserum provided by Dr. T. J. Benraad, Catholic University, Nijmegen, The Netherlands. Assays of ACTH and prolactin were performed as described earlier (26).

Culture of MCF-7 Cells

After trypsinization, cells were preincubated in T25 flasks (Falcon, Becton Dickinson, Naarden, The Netherlands) for 24 hours in medium RPMI 1640 (containing phenol red) supplemented with 10% fetal calf serum (both from Flow Laboratories Ltd, Irvine, Ayrshire, Scotland), penicillin (10,000 U/ml), streptomycin (10,000 μg/ml), and glutamine (2 mM) (all from Biochem, Seromed Products, Berlin, Federal Republic of Germany). After preincubation the medium was changed to medium supplemented with 10% dextran-coated charcoal-treated human (male) serum which contained mifepristone (3.6×10^{-8} M) or tamoxifen (4×10^{-8} M) or estradiol (8×10^{-11} M), or the same concentration of estradiol plus mifepristone or tamoxifen. Media were renewed every other day. After 7 days of culture, media were discarded. Cells were washed with saline and dissolved in 1 M NaOH. The amounts of protein (27) and DNA (28) were determined in each flask. Incubations were done with six or 12 flasks per incubation condition.

Statistical Evaluation of Results

The significance of differences between the results obtained in the various treatment groups was calculated using Wilcoxon's test.

RESULTS

Effects of Prophylactic Treatment on Body Weight and Tumor Latency Period

Prophylactic treatment of immature rats with mifepristone (10 mg/kg/day) during 3 weeks caused significantly lower body weight increment (approximately 5% lower body weight) during the treatment period, while 2 weeks after the last mifepristone injection body weights of rats in control and treated groups were no longer significantly different (results not shown). No toxic side effects due to mifepristone were observed during this prophylactic treatment period, based on the apparently normal alertness and liveliness of the animals. The first appearance of the mammary tumors after the first administration of the DMBA solution was significantly delayed after mifepristone treatment: in control animals tumors were detected after 39 ± 5 days (n = 75, range, 35-56 days), while in mifepristone-treated animals, tumors were first detected after 81 ± 16 days (n = 17), range, 56-114 days; means ± SD; $P < 0.005$).

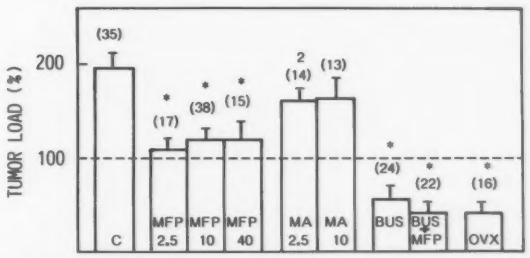

FIGURE 1.—Relative effects on mammary tumor load of different endocrine treatments for 3 wks with mifepristone (MFP), megestrol acetate (MA) (dosages in mg/kg/day), buserelin (BUS), buserelin with mifepristone (10 mg/kg) (BUS + MFP), and ovariectomy (OVX); C = control. Results are means ± SEM (n). Initial tumor load = 100%. 2: $P < 0.05$, *: $P < 0.005$, vs control. No statistical difference between BUS and OVX or between BUS and BUS + MFP.

Effects of Treatments on Tumor Load

The relative effects of various dosages of mifepristone or megestrol acetate, or of buserelin, the combination of mifepristone and buserelin, and ovariectomy on tumor load are shown in figure 1. Mifepristone treatment caused inhibition of tumor growth. Again, no toxic side effects of the three dosages used were observed based on the apparently normal behavior of the animals. Inhibition of tumor growth by the dosages of mifepristone used was approximately 80%-90%. Megestrol acetate in the same dosages also inhibited tumor growth, but to a lower extent (approximately 40%). Mifepristone was significantly more potent than megestrol acetate with all dosages tested ($P < 0.01$ when comparing the effect of the same dose). There was no clear dose-response relationship with the three dosages of mifepristone or the two dosages of megestrol acetate studied. After ovariectomy or treatment with buserelin, tumor remission to 40%-55% of the tumor load at the start of treatment was observed. Combined treatment with buserelin and mifepristone resulted in the same tumor remission as caused by ovariectomy. However, the effects of the latter treatments on tumor load were not significantly different from the results obtained after treatment with buserelin alone.

Effects on Steroid Receptors Present in Mammary Tumors

These effects are shown in table 1. All treatments resulted in a significant reduction in the amount of cytosolic PR, as assessed by Scatchard analysis. Megestrol acetate treatment caused an increase in the cytosolic ER content of the mammary tumors, while all other treatment modalities resulted in a suppression of the amount of ER. The most pronounced effects on cytosolic ER and PR content were observed with the 10 mg/kg and 40 mg/kg dosages of mifepristone, and after combined treatment with buserelin and mifepristone. The effects on both steroid receptors observed after buserelin treatment or ovariectomy were similar.

TABLE 1.—Effects of different treatments on absolute and relative amounts of ERs and PRs present in rat mammary tumor tissue*

Treatment	ER (fmol/mg)	%	PR (fmol/mg)	%
Control	118 ± 57 (33)	100	308 ± 236 (32)	100
Mifepristone				
2.5 mg/kg/day	49 ± 32 (17)†	42	80 ± 100 (17)†	26
10 mg/kg/day	43 ± 31 (38)†	36	3 ± 13 (38)†	1
40 mg/kg/day	60 ± 32 (15)†	51	0 ± 0 (15)†	0
Megestrol acetate				
2.5 mg/kg/day	159 ± 57 (14)‡	135	145 ± 154 (14)†	47
10 mg/kg/day	157 ± 65 (14)‡	133	169 ± 145 (14)‡	55
Buserelin				
40 μg/kg/day	90 ± 57 (22)‡	76	63 ± 78 (21)†	20
Buserelin + mifepristone				
10 mg/kg/day	59 ± 28 (13)†,§	50	0 ± 0 (12)†,¶	0
Ovariectomy	76 ± 50 (13)†	64	16 ± 29 (12)†	5

*Results are means ± SD (*n*).
†Significance vs control: $P < 0.005$.
‡Significance vs control: $P < 0.05$.
§Significance vs buserelin treatment: $P < 0.05$.
¶Significance vs buserelin treatment: $P < 0.005$.

The addition of mifepristone to treatment with buserelin (the combined treatment) lowered the amount of ER and PR significantly more than was observed after single buserelin treatment ($P < 0.05$ and $P < 0.005$, respectively).

Effects on Organ Weights

Mifepristone gave rise to increased weights of the pituitary, ovaries and uterus, while adrenal weights were not affected, not even with the highest dose (table 2). In contrast, treatment with megestrol acetate caused reduced weight of all four organs investigated.

Ovariectomy and buserelin treatment resulted in reduced weights of the uterus and the ovaries; pituitary weight was not changed. After buserelin treatment a small increase was noted for the adrenal weight; ovariectomy had no such effect. However, the combined treatment with mifepristone (10 mg/kg) plus buserelin resulted in a very large increment in adrenal weight ($P < 0.005$ vs control and vs buserelin treatment), while the weight of the uterus was reduced. No change was noted for the weight of the pituitary and the ovaries after treatment with the combination of both drugs.

Effects on Plasma Hormone Concentrations

Mifepristone treatment (10 mg/kg) gave rise to twofold- to sixfold-increased levels of LH, estradiol, prolactin, and progesterone (fig 2). No effects were observed on levels of FSH, ACTH, or corticosterone. However, megestrol acetate treatment (10 mg/kg) caused no change in LH level, but resulted in decreased levels of all other hormones. Similar results were obtained with the 2.5- and 40-mg/kg dosages of mifepristone, and the 2.5-mg/kg dosage of megestrol acetate, respectively (results not shown).

Buserelin treatment and ovariectomy resulted in pronounced increments in LH and FSH concentrations with low concentrations of estradiol and progesterone. In addition, concentrations of prolactin and corticosterone were reduced by ovariectomy or after buserelin treatment. ACTH plasma concentrations were reduced after buserelin treatment.

Changes in Ovarian Histology

Ovaries from control rats ($n = 7$) showed the characteristics of ovaries during normal ovulatory cycles. Autopsy was performed on one rat on the day of ovula-

TABLE 2.—Effects of different treatments on wet weight (mg) of organs isolated from mammary tumor-bearing rats*

Treatment	Pituitary	Adrenals	Ovaries	Uterus
Control	16.4 ± 3.2 (37)	62 ± 14 (39)	157 ± 44 (39)	436 ± 143 (38)
Mifepristone				
2.5 mg/kg/day	18.8 ± 4.0 (17)†	61 ± 13 (17)	175 ± 34 (17)	381 ± 80 (17)
10 mg/kg/day	20.2 ± 3.5 (46)‡	66 ± 17 (45)	184 ± 58 (46)†	542 ± 147 (46)‡
40 mg/kg/day	19.6 ± 3.8 (15)‡	64 ± 9 (15)	207 ± 62 (15)§	471 ± 144 (15)
Megestrol acetate				
2.5 mg/kg/day	13.2 ± 2.2 (15)‡	47 ± 17 (15)‡	120 ± 23 (15)‡	285 ± 79 (15)‡
10 mg/kg/day	13.8 ± 2.5 (13)§	41 ± 9 (13)‡	111 ± 19 (13)‡	361 ± 134 (13)†
Buserelin				
40 μg/kg/day	15.7 ± 3.0 (33)	68 ± 13 (33)†	132 ± 48 (33)‡	268 ± 66 (33)‡
Buserelin + mifepristone				
10 mg/kg/day	16.7 ± 1.9 (23)	84 ± 17 (23)‡,¶	149 ± 41 (23)	280 ± 46 (23)‡
Ovariectomy	16.6 ± 3.4 (21)	62 ± 8 (21)	—	233 ± 53 (20)‡

*Results are means ± SD (*n*).
†Significance vs control: $P < 0.05$.
‡Significance vs control: $P < 0.005$.
§Significance vs control: $P < 0.01$.
¶Significance vs buserelin treatment: $P < 0.005$.

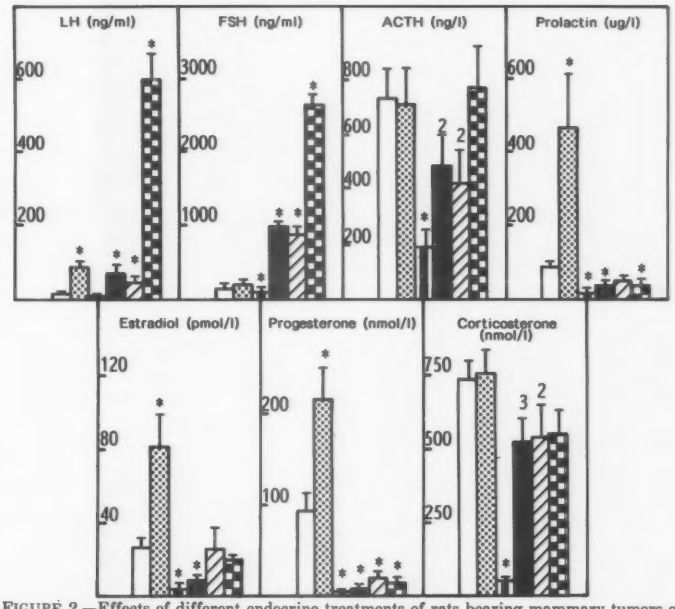

FIGURE 2.—Effects of different endocrine treatments of rats bearing mammary tumors on plasma hormone concentrations. □ = control ($n = 20$–21); ⊡ = mifepristone (10 mg/kg; $n = 23$); ◧ = megestrol acetate (10 mg/kg; $n = 7$); ■ = buserelin ($n = 18$); ▨ = buserelin + mifepristone (10 mg/kg) ($n = 8$); ◪ = ovariectomy ($n = 15$). Results are means ± SEM. 2: $P < 0.05$, 3: $P < 0.01$, *: $P < 0.005$, all vs control.

tion and the other rats were killed during diestrus. No rat in this control group was in proestrus at the time of autopsy.

In mifepristone-treated rats (10 mg/kg/day; $n = 7$), no sign of recent ovulation was observed in the ovaries. All ovaries showed large follicles which were comparable to those at proestrus of normal cycles, with respect to size and histological appearance (diameter > 600 μm; presence of a well-developed granulosa wall). Moreover, ovaries from six treated rats showed very large cystic follicles (diameter > 1000 μm; with atrophied granulosa wall) and ovaries from three treated rats showed extremely large corpora lutea at some spots.

Ovaries from rats treated with buserelin, with or without mifepristone (both treatments, $n = 8$), did not contain large follicles. Few antral follicles were present and their diameters did not exceed 300 μm. In addition, large numbers of corpora lutea were present with a size mostly smaller than that found during diestrus of normal cycles. All ovaries showed a number of "luteinized follicles," ie, follicles showing signs of recent exposure to high levels of LH (such as granulosa cell luteinization and trapped mature oocytes). No difference was recorded between the ovaries from rats treated with buserelin alone, or treated with buserelin and mifepristone.

In Vitro Effects of Mifepristone on Growth of MCF-7 Cells

The effects of mifepristone, estradiol, and tamoxifen on the growth of MCF-7 cells are depicted in figure 3. No effect of mifepristone was found on growth of unstimulated MCF-7 cells based on the amount of protein per culture flask. However, estradiol-stimulated growth was fully abolished ($P < 0.005$) in the presence of mifepristone. The same results were obtained in the presence of tamoxifen with or without estradiol.

Similar results were found on the basis of the amount of DNA (results not shown).

DISCUSSION

The present report describes the first study on the effects of the new steroid antagonist mifepristone on the growth of DMBA-induced rat mammary tumors. The results show that both prophylactic treatment and treatment of rats bearing mammary tumors with mifepristone cause a significant inhibition of tumor growth. No clear dose-response relationship was observed with the doses of mifepristone used.

A comparison of the effects of progestin and antiprogestin treatment showed that inhibition of mammary tumor growth was more pronounced after mifepristone treatment than after megestrol acetate treatment, as also observed in rats with experimental pituitary tumors (26). Organ weights were increased after mifepristone treatment and decreased after megestrol acetate treatment. Similar observations were made with respect to the plasma concentrations of those hormones affected by treatment with either agent.

Mifepristone can also exhibit antiglucocorticoid ef-

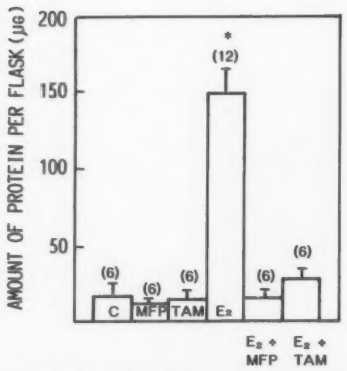

FIGURE 3.—Effects of mifepristone (3.8×10^{-8} M), estradiol (8×10^{-11} M), and tamoxifen (4×10^{-8} M) on the growth of MCF-7 cells. For details on incubation conditions, *see* Materials and Methods section. C = control; MFP = mifepristone; TAM = tamoxifen; E2 = estradiol. Results are means ± SD (*n*). *: $P < 0.005$ vs control.

fects (29,30), but our results in the DMBA model clearly show an antiprogestin activity without an apparent antiglucocorticoid activity. It is difficult to explain the absence of an antiglucocorticoid effect after mifepristone treatment in our model. Perhaps mifepristone is metabolized to a molecule which has a very low affinity for the glucocorticoid receptor.

The growth inhibition of MCF-7 cells caused by mifepristone in the culture medium indicates that the main mechanism of action of mifepristone may reside in a direct antiprogestational effect at the level of the mammary tumor cells after binding to the PR since mifepristone does not bind to the ER (M. Moguilewsky and D. Philibert, unpublished results). Our results are in agreement with the findings of Bardon et al (20), who observed that mifepristone inhibited function and growth *only* in PR-positive mammary tumor cell lines. Perhaps the inhibitory effects of mifepristone on estradiol-stimulated growth of mammary tumor cells involve increased metabolism of estradiol (31), or inhibitory effects on estradiol-induced PR synthesis.

In general, the cytosolic steroid hormone receptor content of the mammary tumors was decreased after treatment. The higher plasma steroid levels after mifepristone treatment may have caused the receptors to bind strongly to the nucleus, in a form which is not recovered in the cytosol preparations. In addition, occupancy of the PR by mifepristone or megestrol acetate may have caused the decreased amount of measurable PR because the assays were not performed under exchange conditions. The effects of buserelin treatment on ER and PR content of the tumors were much greater than those described by Turcot-Lemay et al (32) after treatment of mammary tumor-bearing rats with a different LHRH analog, and might be caused by the decrease in plasma estradiol and progesterone concentrations leading to decreased receptor synthesis.

Increased gonadotropin plasma levels and castrate steroid hormone plasma levels reflect the (medical) castration resulting from ovariectomy and buserelin treatment. These changes in plasma steroid hormone concentrations and the ensuing effect of decreased prolactin concentration may have caused the observed tumor remission (21). Similarly increased LH and FSH plasma levels have been described by Johnson et al (33) after treatment of normal immature rats for 55 days with a different LHRH analog. The decreased ovarian steroid secretion despite increased plasma gonadotropin levels might be explained by the absence of LHRH pulsatility and/or down-regulation of FSH receptors in the ovaries. Increased gonadotropin and low steroid hormone plasma levels after buserelin treatment in the rat are at variance with the situation in the human. Buserelin treatment of breast cancer patients resulted in low plasma levels of both steroid hormones and gonadotropins (11,12). Mifepristone treatment resulted in a significant inhibition of mammary tumor growth, despite increased hormone levels. The inhibition of tumor growth may be explained by a direct inhibitory action of mifepristone at the level of the mammary tumor cells (20). In fact, in the rat high plasma levels of steroid hormones and prolactin in particular may have partly counteracted the direct inhibitory effect of mifepristone at the cellular level.

Treatment with mifepristone influenced ovarian activity as shown by histological examination of the ovaries: normal ovarian cycles appeared to be suspended. Ovaries from rats which were treated with mifepristone contained large follicular cysts and extremely large corpora lutea. The mechanism underlying these effects in relation to increased steroid levels is discussed in a separate paper (34). Apart from direct effects of mifepristone on ovarian function, indirect effects may involve the observed increase in prolactin concentration, since prolactin is known to stimulate ovarian progesterone production in the rat (35).

In contrast, treatment with buserelin resulted in complete absence of mature ovarian follicles. These follicles are the source of the high blood levels of estrogens at proestrus of normal cycles (36). The absence of this kind of follicles can account for the low levels of estradiol measured in plasma of buserelin-treated animals. The decrease in plasma estradiol concentration during buserelin treatment may explain the concomitant decrease in plasma prolactin levels. The absence of mature ovarian follicles indicates that no ovulation and ensuing luteinization takes place. By consequence, low (castrate) amounts of progesterone will be produced in the ovaries.

Whatever may be the mechanism of action of mifepristone with respect to the changes in the ovarian activity, the results of combined treatment with buserelin indicate that the action of mifepristone on ovarian function can be completely abolished by buserelin.

CONCLUSION

Our results show that this new treatment modality with mifepristone, the first available antiprogestin,

caused clear growth inhibition of rat mammary tumors. Because of the observed interaction of mifepristone with rat ovarian functions [although different from the inconsistent findings of short-term treatment in women (19)], it appears more attractive to use this new drug in treatment of postmenopausal patients, or in combination with an LHRH agonist.

REFERENCES

1. MCGUIRE WL, CHAMNESS GC, COSTLOW ME, ET AL. Progress in endocrinology and metabolism. Hormone dependence in breast cancer. Metabolism 23:75–100, 1974.
2. LEGHA SS, and BLUMENSCHEIN GR. Systemic therapy of metastatic breast cancer: a review of the current trends. Oncology 39:140–145, 1982.
3. BROOKS SC, and SINGHAKOWINTA A. Steroid hormones in breast cancer. Spec Top Endocrinol Metab 4:29–67, 1982.
4. ENGELSMAN E. Therapy of advanced breast cancer: a review. Eur J Cancer Clin Oncol 19:1775–1778, 1983.
5. PARIDAENS RJ, LECLERCQ G, and HEUSON JC. Steroid hormones, analogs and antagonists. *In* Cancer Chemotherapy (Pinedo HM, and Chabner BA, eds). Amsterdam, The Netherlands, Elsevier, 1984, pp 170–180.
6. LIPPMAN ME. Growth regulation of human breast cancer. Clin Res 83:375–382, 1985.
7. HORWITZ KB, WEI LL, SEDLACEK SM, ET AL. Progestin action and progesterone receptor structure in human breast cancer: a review. Recent Prog Horm Res 41:249–316, 1985.
8. KLIJN JGM. Hormonal manipulation of cancer: peptides, growth factors and new (anti)steroidal agents. Cancer J 1:191–193, 1986.
9. VAN GILSE HA. Long-term treatment with corticosteroids of patients with metastatic breast cancer. Cancer Chemother Rep 16: 293–298, 1962.
10. SANTEN RJ. Current status of aromatase inhibitors for treatment of breast cancer: new perspectives. *In* Proceedings of the International Symposium on Hormonal Manipulation of Cancer: Peptides, Growth Factors and New (Anti)Steroidal Agents (Klijn JGM, Paridaens R, and Foekens JA, eds). EORTC Monograph Series, New York, Raven Press, vol 18, 1987, pp 71–80.
11. KLIJN JGM, DE JONG FH, LAMBERTS SWJ, ET AL. LHRH-agonist treatment in clinical and experimental human breast cancer. J Steroid Biochem 23:867–873, 1985.
12. MANNI A, SANTEN R, HARVEY H, ET AL. Treatment of breast cancer with gonadotropin-releasing hormone. Endocr Rev 7:89–94, 1986.
13. PLANTING AST, ALEXIEVA-FIGUSCH J, BLONK-VAN DER WIJST J, ET AL. Tamoxifen therapy in premenopausal women with metastatic breast cancer. Cancer Treat Rep 69:363–368, 1985.
14. ALEXIEVA-FIGUSCH J, VAN PUTTEN WLJ, VAN GILSE HA, ET AL. Sequential treatment of metastatic breast cancer with tamoxifen after megestrol acetate therapy and vice versa (a retrospective study). Med Oncol Tumor Pharmacother 2:69–75, 1985.
15. ALEXIEVA-FIGUSCH J, BLANKENSTEIN MA, HOP WCJ, ET AL. Treatment of metastatic breast cancer patients with different dosages of megestrol acetate: dose relations, metabolic and endocrine effects. Eur J Cancer Clin Oncol 20:33–40, 1984.
16. ALEXIEVA-FIGUSCH J, DE JONG FH, LAMBERTS SWJ, ET AL. Alternating and combined treatment with tamoxifen and progestins in postmenopausal breast cancer. *In* Proceedings of the International Symposium on Hormonal Manipulation of Cancer: Peptides, Growth Factors and New (Anti)Steroidal Agents (Klijn JGM, Paridaens R, and Foekens JA, eds). EORTC Monograph Series, New York, Raven Press, vol 18, 1987, pp 145–155.
17. SETYONO-HAN B, HENKELMAN MS, FOEKENS JA, ET AL. Direct inhibitory effects of somatostatin (analogues) on the growth of human breast cancer cells. Cancer Res 47:1566–1570, 1987.
18. SHORTLE B, DYRENFURTH I, and FERIN M. Effects of an antiprogesterone agent, RU486, on the menstrual cycle of the rhesus monkey. J Clin Endocrinol Metab 60:731–735, 1985.
19. SCHAISON G, GEORGE M, LESTRAT N, ET AL. Effects of the antiprogesterone steroid RU486 during midluteal phase in normal women. J Clin Endocrinol Metab 61:484–489, 1985.
20. BARDON S, VIGNON F, CHALBOS D, ET AL. RU486, a progestin and glucocorticoid antagonist, inhibits the growth of breast cancer cells via the progesterone receptor. J Clin Endocrinol Metab 60: 692–697, 1985.
21. JORDAN VC. Laboratory studies to develop general principles for the adjuvant treatment of breast cancer with antiestrogens: problems and potential for future clinical applications. Breast Cancer Res Treat 3(suppl):73–86, 1983.
22. BLANKENSTEIN MA, PETERS-MECHIELSEN MJ, MULDER E, ET AL. Estimation of the total estrogen receptors in DMBA-induced rat mammary tumors by exchange of nuclear bound ligand at low temperature: a comparison with rat uterus. J Steroid Biochem 13:557–564, 1980.
23. EORTC BREAST CANCER COOPERATIVE GROUP. Revision of the standards for the assessment of hormone receptors in human breast cancer. Eur J Cancer 16:1513–1515, 1980.
24. WELSCHEN R, OSMAN P, DULLAART J, ET AL. Levels of follicle-stimulating hormone, luteinizing hormone, oestradiol-17 and progesterone, and follicular growth in the pseudopregnant rat. J Endocrinol 64:37–47, 1975.
25. DE JONG FH, BAIRD DT, and VAN DER MOLEN HJ. Ovarian secretion rates of oestrogens, androgens and progesterone in normal women and in women with persistent ovarian follicles. Acta Endocrinol (Copenh) 77:575–587, 1974.
26. LAMBERTS SWJ, UITTERLINDEN P, BONS EG, ET AL. Comparison of the actions of RU38486 and megestrol acetate in the model of a transplantable adrenocorticotropin- and prolactin-secreting rat pituitary tumor. Cancer Res 45:1015–1019, 1985.
27. BRADFORD MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 72:248–254, 1976.
28. SETARO F, and MORLEY CGD. A modified fluorimetric method for the determination of microgram quantities of DNA from cell or tissue cultures. Anal Biochem 71:313–317, 1976.
29. BERTAGNA X, BERTAGNA C, LUTON JP, ET AL. The new steroid analog RU486 inhibits glucocorticoid action in man. J Clin Endocrinol Metab 59:25–28, 1984.
30. GAGNE D, PONS M, and PHILIBERT D. RU38486: a potent anti-glucocorticoid in-vitro and in-vivo. J Steroid Biochem 23:247–251, 1985.
31. MAUVAIS-JARVIS P, KUTTENN F, and GOMPEL A. Antiestrogen action of progesterone in breast tissue. Breast Cancer Res Treat 8:179–187, 1986.
32. TURCOT-LEMAY L, CUSAN L, SEQUIN C, ET AL. Effect of an LHRH analog on growth and hormone receptor levels in DMBA-induced mammary tumors in the rat. J Recept Res 2:135–151, 1981.
33. JOHNSON ES, GENDRICH RL, and WHITE WF. Delay of puberty and inhibition of reproductive processes in the rat by a gonadotropin-releasing hormone agonist analog. Fertil Steril 27:853–860, 1976.
34. VAN DER SCHOOT P, BAKKER GH, and KLIJN JGM. Effects of the progesterone antagonist RU486 (mifepristone) on ovarian activity in the rat. Endocrinol, in press, 1987.
35. FREEMAN ME, and NEILL JD. The pattern of prolactin secretion during pseudopregnancy in the rat: a daily nocturnal surge. Endocrinol 90:1292–1294, 1972.
36. UILENBROEK JTJ, and RICHARDS JS. Ovarian follicular development during the rat estrous cycle: gonadotropin receptors and follicular responsiveness. Biol Reprod 20:1159–1165, 1979.

High-Dose Pulse Chlorambucil in Advanced, Low-Grade Non-Hodgkin's Lymphoma[1]

Carol S. Portlock,[2,*] David S. Fischer,[2] Ed Cadman,[3] W. Bruce Lundberg,[2] Arthur Levy,[2] Samuel Bobrow,[2] Joseph R. Bertino,[4] and Leonard Farber[2]

High-dose pulse chlorambucil was given orally at a dose of 16 mg/m^2 daily for 5 consecutive days each month, as reported by Cadman et al. It was used to treat 33 patients with advanced, low-grade non-Hodgkin's lymphoma. With median follow-up of 4.2+ years, 70% of the patients achieved objective response. Eleven of 24 patients with follicular small cleaved cell lymphoma (FSCL) had pathological complete response; nine of 24 with FSCL and three of seven with small lymphocytic lymphoma had partial response. Median disease-free survival was 28 months. Actuarial survival for all patients was 60% at 5 years from initiation of therapy. Treatment toxicity was minimal. Pulse chlorambucil is an effective and minimally toxic palliative therapy for advanced FSCL. [Cancer Treat Rep 71:1029–1031, 1987]

In 1982, Cadman et al (1) reported preliminary experience with high-dose pulse chlorambucil (pCBL) in 18 patients with advanced nodular lymphocytic poorly differentiated lymphoma. The regimen was found to induce clinical remission rapidly and frequently (78%) and was well tolerated, with minimal acute and chronic toxicity. Unlike other previously published reports of single-agent therapy in advanced indolent lymphoma (2), high-dose pCBL was reported to yield apparently durable remission with no relapse evident at a median follow-up of 35 months.

It is the purpose of this report to update this original Yale experience with high-dose pCBL. Follow-up for all patients ranges from 0.5 to 9+ years (median, 4.2+) in 33 patients with advanced low-grade non-Hodgkin's lymphoma.

METHODS

From February 1977 through February 1984, 33 patients with low-grade lymphoma entered in the Yale Tumor Registry were treated with pCBL. The drug regimen was pCBL given orally at a dose of 16 mg/m^2 daily for 5 consecutive days each month for 12–24 months (1).

Characteristics of the patients treated are shown in table 1. There were 16 males and 17 females with a mean age of 53.7 years. All pathology was reviewed at Yale and reported according to the Rappaport classification (3) and the working formulation (4). Complete clinical staging is reported according to the Ann Arbor system (5) and included complete history and physical examination; chest x-ray; abdominal evaluation with lymphogram, ultrasound, and/or computerized tomography; and bone marrow biopsy. Four patients received prior or concurrent irradiation; one patient had previously received chemotherapy. Seven patients in clinical complete remission following at least 1 year of pCBL received low-dose irradiation (1500–2000 rad) to prior sites of disease involvement according to a prospective protocol. This adjuvant radiotherapy was based on the experience of Farber et al (6) in the combined modality therapy of advanced Hodgkin's disease.

Response to treatment was assessed prior to each course of pCBL and every 2–4 months thereafter. Partial response (PR) was defined as a decrease in all tumor masses $\geq$ 50% for 2+ months. Clinical complete response (cCR) was defined as complete disappearance of all known disease other than that in the bone marrow, for $\geq$ 2 months. Pathological complete response (pCR) was defined as cCR plus the absence of bone marrow involvement. Patients with progressive disease were considered to have treatment failure and received other therapy. Responding patients received pCBL for a minimum of 12 months and a maximum of 24 months. If pCR was documented at $\geq$ 12 months, treatment was discontinued.

All actuarial calculations are reported according to the method of Kaplan and Meier (7). Overall survival was measured from the date of initiation of pCBL; disease-free survival of complete responders was measured from the discontinuation of pCBL to relapse.

[1] Received Mar 20, 1987; revised July 24, 1987; accepted July 30, 1987.
[2] Yale University School of Medicine, New Haven, CT.
[3] The University of California, San Francisco.
[4] Memorial Sloan-Kettering Cancer Center, New York, NY

*Reprint requests to: Carol S. Portlock, MD, Division of Medical Oncology, Yale University School of Medicine, Rm NS 294D, 333 Cedar St, New Haven, CT 06510.

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Total	33
Sex	
Male	16
Female	17
Age (yrs)	
Mean: 53.7	
Range: 20–85	
Histology	
FSCL	24
FML	2
SL	7
Stage	
II	4
III	8
IV	21
Symptoms	
A	31
B	2
Radiotherapy	
Prior	4
Adjuvant	7

RESULTS

Response to Therapy

Median follow-up for all patients was 4.2+ years. Objective response was seen in 23 of 33 patients: pCR in 11 and PR in 12. The median time to achievement of pCR was 12 months. Response according to histology was as follows: for follicular small cleaved cell lymphoma (FSCL), pCR in 11 patients (46%), PR in nine, and no response (NR) in four; for follicular mixed lymphoma (FML), NR in two; and for SL (small lymphocytic lymphoma), PR in three and NR in four.

Duration of Response and Survival

The actuarial disease-free survival of complete responders is seen in figure 1. Median time to relapse was 28 months. Two responders remain relapse-free for 18+ months. Of the five pCR patients receiving adjuvant irradiation, four have relapsed at 18–42 months after discontinuation of therapy and one remains in pCR at 22+ months.

Actuarial survival for all patients was 60% at 5+ years. Six patients developed biopsy-proven transformation to an aggressive non-Hodgkin's lymphoma (one, diffuse mixed; two, follicular; and three, diffuse, large cell). One patient died of acute nonlymphocytic leukemia and one of non-small cell lung cancer.

Toxicity

The pCBL was well tolerated. Hematologic toxicity was minimal, as previously described by Cadman et al (1). One patient developed significant thrombocytopenia (nadir, 50,000 cells/mm^3), requiring discontinuation of therapy, but with recovery over 2 months. One patient developed localized herpes zoster, which resolved without complication. There were no significant infections requiring hospitalization and no bleeding complications among the 33 patients treated.

Two female patients developed drug-induced premature menopause at ages 38 and 41. No other chronic toxic effects of pCBL were evident.

Two patients developed second neoplasms. A 49-year-old man with stage IVA FSCL who was unresponsive to 6 months of pCBL and required multiagent chemotherapy and irradiation died of acute nonlymphocytic leukemia and progressive lymphoma 3.5 years after initial pCBL. A 65-year-old man with SL (stage IVB) who had stable disease for 3 years while receiving pCBL died of non-small cell lung cancer 3.5 years after initial pCBL.

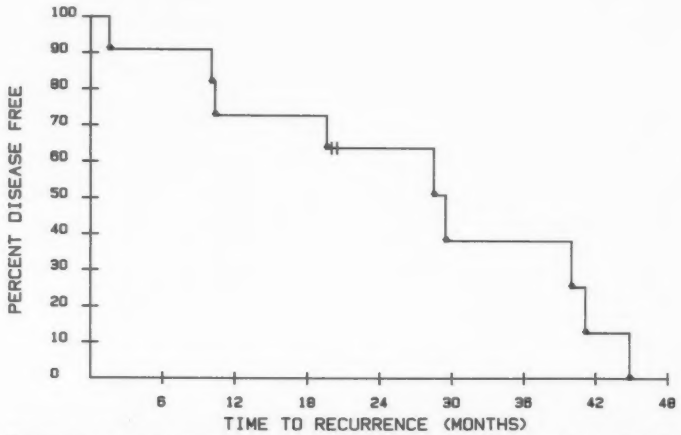

FIGURE 1.—Actuarial disease-free survival (0–0) of 11 complete responders treated with pCBL.

DISCUSSION

Pulse Chlorambucil

High-dose pCBL given orally at a dose of 16 mg/m^2 daily for 5 consecutive days each month for 1–2 years achieved a high rate of objective clinical response. In this series of 33 patients with advanced low-grade lymphoma, 11 achieved pCR and 12 had PR, for an objective response rate of 70%. Complete response was seen in 11 of 24 patients with FSCL; none of two with FML and none of seven with SL had complete response. The median time to achievement of pCR was 12 months.

These complete response data for FSCL (46%) are similar to those reported by others for daily therapy with a single alkylating agent in advanced low-grade lymphoma. The investigators at Stanford University, CA (2), have reported pCR rates of 65% using daily cyclophosphamide or chlorambucil in two prospective trials; in one trial, the median time to pCR was 24 months. Lister et al (8) reported cCR in 13% of the patients receiving chlorambucil daily for 14 weeks. Kennedy et al (9) achieved pCR in 47% of the patients receiving sequential daily cyclophosphamide, vincristine, and prednisone. Although the numbers are small, none of the seven patients with SL achieved pCR to pCBL. In other studies of single-agent therapy, either this histology was excluded from protocol entry (9) or results were not reported separately (2).

With a median follow-up of 4.2+ years, the disease-free survival in this series was 28 months; only two of 11 complete responders remain free of disease progression at 1.5+ years (fig 1). In a previous report (1), no relapses were seen among 13 patients with cCR or pCR, with a median follow-up of 35 months. These contrasting data simply serve to illustrate the importance of prolonged follow-up in these indolent diseases.

Other investigators have also reported the lack of durable remission with therapy using single alkylating agents. Median relapse-free survival times of 50 months (2), 25+ months (9), and 12 months (8) without apparent plateau are illustrative.

In an attempt to improve relapse-free survival among patients with pCR, five pCR patients received low-dose irradiation (1500–2000 rad) to sites of disease involvement present at chemotherapy initiation. This combined modality approach was based on the studies of Farber et al (6) in the successful treatment of advanced Hodgkin's disease. Only one of five patients remains in remission at 22+ months following discontinuation of therapy; four have relapsed at 18–42 months.

Although disease-free survival has not been durable following single-agent chemotherapy, overall survival has been good in all reports. In this series, 60% of the patients remain alive at 5+ years. Median survival times of 5+ years (2), 30 months (9), and 48+ months (8) are typical of other groups.

The acute toxicity of high-dose pCBL was minimal, confirming earlier results (1). Chronic myelosuppression after therapy was not seen. Second neoplasms were documented in two patients: non-small cell lung cancer and acute nonlymphocytic leukemia in a nonresponder after multiple chemotherapy regimens and irradiation. These toxic effects compare favorably to those associated with daily cyclophosphamide, which may produce alopecia and hemorrhagic cystitis, and other acute and chronic toxic effects are similar. In addition, pCBL may be more convenient to administer and monitor than daily chlorambucil.

REFERENCES

1. CADMAN E, DRISLANE F, WALDRON JA, JR, ET AL. High dose pulse chlorambucil: effective therapy for rapid remission induction in nodular lymphocytic poorly differentiated lymphoma. Cancer 50:1037–1041, 1982.
2. PORTLOCK CS. Good risk, non-Hodgkin's lymphomas: approaches to management. Semin Hematol 20:25–34, 1983.
3. RAPPAPORT H, WINTER WJ, and HICKS EB. Follicular lymphoma—a re-evaluation of its position in the scheme of malignant lymphoma, based on a survey of 253 cases. Cancer 9:792–821, 1956.
4. The Non-Hodgkin's Lymphoma Pathologic Classification Project: National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphoma: summary and description of a working formulation for clinical usage. Cancer 49:2112–2135, 1982.
5. CARBONE PP, KAPLAN HS, MUSSHOFF K, ET AL. Report of the committee on Hodgkin's disease staging classification. Cancer Res 31:1860–1861, 1971.
6. FARBER L, PROSNITZ L, CADMAN EC, ET AL. Curative potential of combined modality therapy for advanced Hodgkin's disease. Cancer 46:1509–1517, 1980.
7. KAPLAN ES, and MEIER P. Nonparametric estimation from incomplete observations. Am Stat Assoc J 53:457–480, 1958.
8. LISTER TA, CULLEN MH, BEARD MEJ, ET AL. Comparison of combined and single-agent chemotherapy in non-Hodgkin's lymphoma of favorable histological type. Br Med J 1:533–537, 1978.
9. KENNEDY BJ, BLOOMFIELD CD, KIANG DT, ET AL. Combination versus successive single agent chemotherapy in lymphocytic lymphoma. Cancer 41:23–28, 1978.

Improved Survival of Infants Less Than 1 Year of Age With Acute Lymphoblastic Leukemia Treated With Intensive Multiagent Chemotherapy[1,2,3]

Gregory H. Reaman,[4] Peter G. Steinherz,[5] Paul S. Gaynon,[6] W. Archie Bleyer,[7] Jerry Z. Finklestein,[8] Richard Evans,[9] Denis R. Miller,[10] Harland N. Sather,[11] and G. Denman Hammond[11,*]

Infants with acute lymphoblastic leukemia (ALL) have a poor prognosis. Early disease recurrence, rather than excessive toxicity and complications resulting in limitation of therapy, is the major factor responsible for this disappointing outcome. The CCG-192P trial was a groupwide pilot study of the Childrens Cancer Study Group for the treatment of ALL in patients at high risk for relapse, which was defined by wbc count $> 50 \times 10^3/\mu l$ at diagnosis. Because of the recognized poor prognosis, all infants < 1 year of age were entered in this study regardless of wbc count at diagnosis. Therapy included intensive induction and consolidation followed by a cyclic, sequential maintenance program. The CNS prophylaxis consisted of intrathecal chemotherapy and cranial irradiation, which was deferred until patients were > 1 year of age. During the period January 1982 to January 1984, 27 infants ranging in age from 2 days to 11 months who had ALL were entered in this study; 71% had wbc counts $> 50 \times 10^3/\mu l$, and 23% presented with CNS leukemia. Complete remission was achieved in 93% of the patients. The median duration of remission is 17 months. With a median follow-up of 43 months, the life-table estimate of event-free survival (EFS) is 36% at 4 years. A recently reported historical control group of infants with ALL who were treated with previous Childrens Cancer Study Group protocols demonstrated a median remission duration of 8 months and an estimated EFS of only 21% at 4 years. Toxicity and therapy-related complications were not observed more frequently in infants than in older patients treated with this protocol. However, EFS of infants was significantly worse than that of patients > 1 year of age ($P = < 0.001$). All four CNS relapses occurred in patients who had received cranial irradiation. A wbc count $< 50 \times 10^3/\mu l$ at diagnosis demonstrated significance ($P = 0.03$) as a favorable prognostic indicator in this small patient sample. Although these data are preliminary, they suggest that intensive therapy is reasonably well tolerated by infants and results in prolongation of remission duration and improved EFS. [Cancer Treat Rep 71:1033-1038, 1987]

Recent clinical trials in childhood acute lymphoblastic leukemia (ALL) performed by the Childrens Cancer Study Group (CCSG) have demonstrated a uniformly poor prognosis for children < 1 year of age. We have recently reported a retrospective review of all 115 infants < 1 year of age with ALL who were entered in a consecutive series of CCSG leukemia protocols during a 9-year period (1). Results of this analysis demonstrated a significantly increased frequency of adverse clinical features, including hyperleukocytosis, massive hepatomegaly, massive splenomegaly, CNS leukemia at diagnosis, hypogammaglobulinemia, and marked thrombocytopenia. These findings have recently been confirmed by a similar review from the Pediatric Oncology Group (2). In addition, an increased frequency of adverse immunophenotypes of leukemic lymphoblasts (2) as well

[1] Received Dec 19, 1986; revised July 13, 1987; accepted July 30, 1987.
[2] Supported by Public Health Service grants (CA) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. *See* Appendix.
[3] Presented in part at the annual meeting of the American Society of Clinical Oncology, Houston, TX, May 19-21, 1985.
[4] Children's Hospital National Medical Center, Washington, DC.
[5] Memorial Sloan-Kettering Cancer Center, New York, NY.
[6] Wyler Children's Hospital, Chicago, IL.
[7] Children's Hospital and Medical Center, Seattle, WA.
[8] Harbor/University of California at Los Angeles Medical Center, Torrance.
[9] Mayo Clinic, Rochester, MN.
[10] Children's Memorial Hospital, Chicago, IL.
[11] University of Southern California School of Medicine, Los Angeles.
* *Reprint requests to:* Childrens Cancer Study Group, 199 N Lake Ave, Third Floor, Pasadena, CA 91101.

as cytogenetic abnormalities (3) associated with a poor prognosis (4) have been observed in infants with ALL.

Previous efforts in the treatment of ALL in infants < 1 year of age have resulted in a median duration of complete remission of only 8 months. The life-table estimate of relapse-free survival for infants < 1 year of age is only 23% at 4 years (1). An inordinate rate of complications and excessive toxicity resulting in limitation of therapy were not the only factors in the disappointing outcome of this patient group. Early disease recurrence, which was generally characterized by bone marrow relapse, was the major factor responsible for the extremely poor prognosis. Furthermore, a CNS relapse rate > 20% was observed and did not appear to be appreciably diminished by the use of cranial irradiation.

The present study was undertaken to investigate whether an intensive multiagent chemotherapy program could prolong remission duration and ultimately improve survival for infants < 1 year of age with ALL.

PATIENTS AND METHODS

The CCG-192P trial was a pilot study opened to patient entry in April 1981 for the treatment of ALL in patients with a poor prognosis. Eligibility criteria included the diagnosis of ALL with an initial wbc count $> 50 \times 10^3/\mu l$. Because our experience with infants demonstrated that they represent the group at highest risk for early treatment failure, in August 1983, all infants < 1 year of age, regardless of initial wbc count, were entered in this study. Accrual of infants to this study ended in January 1984, at which time the CCSG initiated a specific clinical trial for infants with ALL. The projected accrual of infants in this protocol was 10 patients per year. Interim analyses of the entire study were performed at 6-month intervals. The rationale, details of the therapy plan, and preliminary treatment results have been reported recently (5). The chemotherapy schedule and doses utilized are shown in table 1.

The dosages of all chemotherapeutic agents utilized for infants were calculated using body weight (6) rather than surface area, which resulted in essentially a 50% reduction of dosages based on body surface area. Other therapy modifications included the deletion of radiation therapy to bulk disease during induction, which was employed in older patients in this study. Furthermore, whole-brain radiotherapy at a dose of 1800 cGy (180 cGy × ten fractions) as part of CNS prophylaxis was delayed until patients were ≥ 1 year of age. Additional intrathecal chemotherapy was given during induction to patients with meningeal leukemia at diagnosis.

The study group includes all 27 infants < 1 year of age with the ALL diagnosis confirmed by morphological and cytochemical criteria including PAS, Sudan black, peroxidase, and nonspecific esterase stains. The infants were registered in this study after parental

TABLE 1.—Chemotherapy protocols

Drug	Dose	Day
	Induction	
Cytarabine	20 mg intrathecally	0
Cyclophosphamide	40 mg/kg iv	0
Prednisone	2 mg/kg orally	1-28
Daunorubicin	2 mg/kg iv	2, 3
Methotrexate	6 mg intrathecally	15, 29
L-Asparaginase	200 IU/kg im	15-28 (Monday, Wednesday, Friday × 6)
Vincristine	0.05 mg/kg iv	1, 8, 15, 22, 29
	Consolidation	
Cytarabine	5 mg/kg iv or sc	0-7
Thioguanine	2.5 mg/kg orally	0-7
Prednisone taper		0-14
Methotrexate	6 mg intrathecally	7, 14, 21, 31
L-Asparaginase	200 IU/kg im	8-19
Methotrexate	0.3 mg/kg iv	20-24
	Maintenance*	
Thioguanine	10 mg/kg orally	0-3
Cyclophosphamide	40 mg/kg iv	4 (20 mg/kg in Cycle 1)
Vincristine	0.05 mg/kg iv	11, 18, 25
Prednisone	6 mg/kg orally	11-17
Methotrexate	5 mg/kg iv in 4-hr infusion	25
Doxorubicin	0.5 mg/kg iv	39, 40
Cytarabine	1.2 mg/kg every 12 hrs sc × 6	41-43
Thioguanine	1 mg/kg orally every 12 hrs × 6	41-43
Methotrexate	6 mg intrathecally	56

*In maintenance therapy, 56-day cycles were repeated for 36 mos of therapy from time of diagnosis.

informed consent was obtained. Patients ranged in age from 2 days to 11 months, with a median age of 6 months. There were 11 males and 16 females. The wbc counts at diagnosis ranged from 8 to 1500 $\times$ $10^3/\mu l$ (median, 100). Nine patients presented with wbc counts $> 50 \times 10^3/\mu l$. Diagnosis of meningeal leukemia was defined by the presence of > 5 mononuclear wbc/μl of cerebrospinal fluid, with confirmatory cytology; it was observed in six patients (incidence, 22%). Massive hepatomegaly and/or splenomegaly was present in 37% of the patients. Morphology (French-American-British classification) was L1 in 18 patients and L2 in seven. The L2 morphology was defined as the presence of $\geq 25\%$ cells exhibiting characteristic L2 morphology (7). There were no patients with T-cell leukemia, as assessed by sheep rbc rosette formation and/or reactivity with monoclonal antibodies to the T-cell-associated antigen (CD2). Pretreatment lymphoblasts of 14 of the 15 patients tested demonstrated no reactivity with monoclonal antibody to the common ALL antigen. The incidence of adverse clinical features at presentation in this group of infants was nearly identical to that observed in our previously reported large series of infants with ALL (1).

The method of Kaplan and Meier (8) was employed to give life-table estimates. The primary outcome index for life-table analysis was the event-free survival period. This is defined as the time from entry in the study to the first occurrence of the following adverse events: death, failure to achieve remission, or relapse in any site following successful remission induction. Life-table comparisons of subgroups were performed with the log-rank statistic (9). The chi-square test for homogeneity of proportions was used to compare clinical characteristics of the historical control and study groups of infants.

RESULTS

Response to Therapy and Outcome

Complete remission was achieved in 25 of the 27 study patients, with an induction rate of 93%. The median remission duration is 17 months. Seven patients have experienced bone marrow relapse, and four who had received whole-brain radiation therapy have experienced isolated CNS relapse. No isolated CNS relapses were observed in infants with meningeal leukemia at diagnosis. One patient experienced an isolated testicular relapse, and one was removed from the study in remission at 8 months for allogeneic bone marrow transplantation. One patient experienced an isolated testicular relapse at completion of initial therapy. Two patients died in remission; nine continue in complete remission. With a median follow-up of 43 months, Kaplan-Meier life-table analysis of event-free survival demonstrates that 36% of the patients are projected to continue free of adverse events at 4 years from diagnosis (fig 1). In contrast, event-free survival at 4 years from diagnosis for patients > 1 year of age treated in this protocol is estimated at 68% ($P < 0.0001$)

The impact of initial wbc count on event-free survival

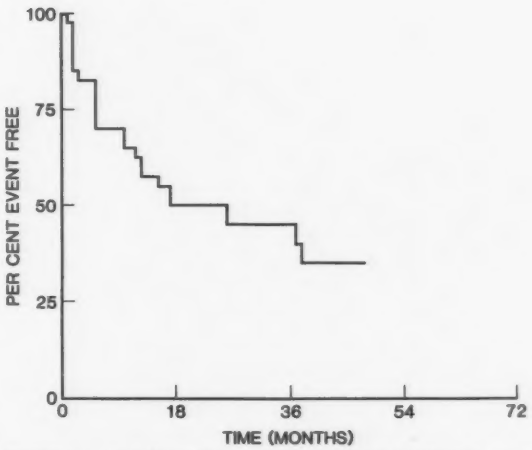

FIGURE 1.—Life-table estimate of event-free survival of infants < 1 yr of age with ALL.

of infants < 1 year of age is demonstrated in figure 2. A wbc count $< 50 \times 10^3/\mu l$ was a statistically significant predictor of more favorable outcome ($P = 0.03$). Comparison by univariate analysis of event-free survival of infants < 6 months of age with that of infants 6–11 months of age also demonstrated a difference in outcome. Event-free survival at 48 months for infants < 6 months of age is 16%, compared to 48% for infants 6–11 months of age. Neither non-L1 morphology nor meningeal leukemia at diagnosis demonstrated significant predictive potential.

Toxicity

Among the 27 patients who were evaluated for induction toxicity, there were three episodes of sepsis (two

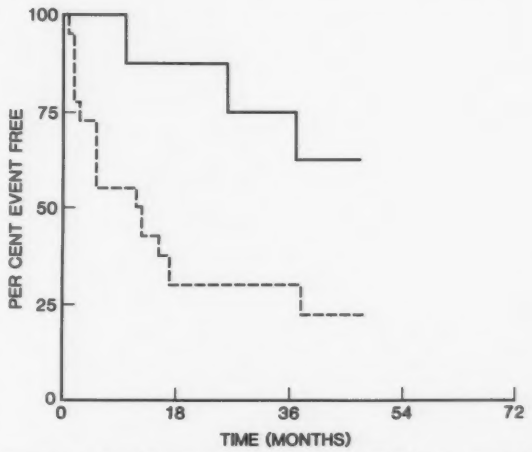

FIGURE 2.—Event-free survival of infants with ALL by wbc count at diagnosis. ——— = < $50 \times 10^3/\mu l$ ($n = 9$). ----- = > $50 \times 10^3/\mu l$ ($n = 18$).

gram negative and one *Staphylococcus aureus*) and one episode of *Pneumocystis carinii* pneumonia despite prophylactic administration of trimethoprim/sulfamethoxazole. Indwelling, tunneled right atrial catheters were utilized for the majority of patients. Two patients with hyperleukocytosis underwent partial exchange transfusion to prevent metabolic complications secondary to tumor cell lysis. No such metabolic complications were observed. Trimethoprim/sulfamethoxazole prophylaxis was recommended. All patients completed this phase of therapy in 28 days, the planned duration of the phase. The median time to recovery of granulocyte count $> 1000/\mu l$ and to recovery of platelet count $> 100,000/\mu l$ was 21 days.

Twenty-five patients were evaluated for toxicity during phase II consolidation therapy. There was one episode of fatal *P. carinii* pneumonia. Thirteen patients experienced severe hematologic toxicity manifested by an absolute neutrophil count $< 500/\mu l$ and/or a platelet count $< 50 \times 10^3/\mu l$. The median time to recovery was 22 days. Three patients exhibited severe mucosal toxicity. All patients completed this phase of therapy during the planned 28 days.

Of the 23 patients evaluated for toxicity during maintenance therapy, eight (34%) experienced severe hematologic toxicity and three (13%) experienced severe mucosal toxicity. Two patients developed documented gram-negative sepsis during maintenance, and one of these episodes proved fatal. Episodes of toxicity were most frequently encountered during Days 45–50 of each maintenance cycle.

The mean percentages of calculated doses actually delivered during induction, consolidation, and maintenance were 94%, 89%, and 86%, respectively.

DISCUSSION

The present study was undertaken to investigate whether an intensive multiagent chemotherapy protocol could result in prolongation of remission duration and, ultimately, have an impact on the survival of infants with ALL. This particular group of patients has the worst prognosis and is at highest risk for early treatment failure.

A complete remission rate of 93% was achieved. This does not represent a difference from the complete remission rate observed in our recent retrospective study (1). However, failure to achieve an initial complete remission does not appear to be the major obstacle to cure for this particular group of patients. Early relapse resulting in a median remission duration of only 8 months with conventional therapy was observed (1). The present clinical trial, utilizing a significantly more intensive approach, has resulted in a median remission duration of 17 months. Furthermore, the life-table estimate of event-free survival demonstrates that 36% of the patients in this study are projected to continue in complete remission at 4 years from diagnosis. Comparison with the historical control group demonstrated that only 21% of the patients had not experienced an adverse event by this point (1). The log-rank test reveals a difference in event-free survival between these groups of patients that approaches significance ($P = 0.06$).

The limitations of utilizing a historical control group in evaluating the present treatment results are recognized. However, the relative infrequency of ALL in children < 1 year of age precludes a comparative study with concurrent therapy strategies. Compared to our recently reported series of infants with ALL, which represents the largest reported series of similarly treated patients < 1 year of age with ALL, the present group of infants is very similar with respect to age distribution and the frequency of adverse clinical characteristics. In fact, the chi-square test for homogeneity of proportions for wbc counts at diagnosis and age distributions demonstrated no significant differences between the two groups ($P = 0.89$; 0.69).

Although the outcome for these intensively treated infants appears to be improved, this study confirms the aggressive nature of ALL in infants < 1 year of age. In fact, the prognosis for infants is significantly worse than that for older children with ALL at high risk for early relapse because of wbc count $> 50 \times 10^3/\mu l$ at diagnosis. One possible explanation for this discrepancy in outcome may be related to the dosage of chemotherapy utilized for infants treated in this protocol. As mentioned, doses for infants < 1 year of age were calculated using body weight rather than body surface area in accordance with earlier suggestions that young infants experienced excessive chemotherapy-related toxicity and complications (6). However, our retrospective review of 115 infants < 1 year of age treated for ALL with conventional therapy at standard doses did not demonstrate an excessive rate of therapy-related complications, with the exception of vincristine-related neurotoxicity (1). Furthermore, significant modifications of protocol-specified dosages impacted unfavorably on outcome. In this study, toxicity and therapy-related complications were not observed more frequently in infants than in patients > 1 year of age who were treated with the same agents utilizing the same schedule. In fact, catastrophic complications were infrequently observed, suggesting that augmentation of doses of intensive chemotherapy requires exploration in infants with ALL.

The present study also demonstrates a difference in event-free survival of infants < 6 months of age, compared to that of infants 6–11 months of age. This difference is accounted for by an excess of relapses in younger infants and not by an increased incidence of either induction failures or deaths in remission. The distribution of patients with wbc counts $> 50 \times 10^3/\mu l$ was similar in both age groups. Evaluation of such biologic variables as blast cell immunophenotype and specific karyotypic abnormalities is being performed in our current clinical trial of ALL in infants.

Although the numbers are extremely small, this study confirms our earlier observation that extramedullary

relapse, particularly CNS relapse, occurs with increased frequency in patients of this age group. The fact that all of the CNS relapses observed in these patients occurred after cranial irradiation, which was deferred until patients reached 1 year of age, again suggests that cranial irradiation, particularly when delayed, fails to provide adequate protection from CNS relapse in this select group of patients.

These data demonstrate that intensive multiagent chemotherapy administered in reduced dosages is tolerated by young infants. Preliminary results of this study suggest that the therapy utilized may result in prolongation of remission duration. We conclude that further investigation of intensive chemotherapy programs and alternative therapy to prevent CNS involvement are warranted to improve the outcome for infants with ALL.

APPENDIX

Principal Investigators of the Childrens Cancer Study Group

Institution	*Investigator*	*Grant No.*
Group Operations Office, University of Southern California Comprehensive Cancer Center, Los Angeles	Denman Hammond John Weiner Harland Sather Richard Sposto Mark Krailo Jonathan Buckley	CA-13539
University of Michigan Medical Center, Ann Arbor	Ruth Heyn	CA-02971
University of California Medical Center, San Francisco	Arthur Ablin	CA-17829
Rainbow Babies and Children's Hospital, Cleveland, OH	Peter Coccia	CA-20320
Children's Hospital National Medical Center, Washington, DC	Gregory Reaman	CA-03888
Children's Memorial Hospital, Chicago, IL	Edward Baum	CA-07431
Children's Hospital of Los Angeles, CA	Jorge Ortega	CA-02649
Children's Hospital of Columbus, OH	Frederick Ruymann	CA-03750
Babies Hospital, New York, NY	Sergio Piomelli	CA-03526
Children's Hospital of Pittsburgh, PA	Vincent Albo	CA-36015
Vanderbilt University School of Medicine, Nashville, TN	John Lukens	CA-26270
Doernbecher Memorial Hospital for Children, Portland, OR	Robert Neerhout	CA-26044
University of Minnesota Health Sciences Center, Minneapolis	Mark Nesbit	CA-07306
University of Texas Health Sciences Center, San Antonio	Thomas Williams	CA-36004
Children's Hospital of Philadelphia, PA	Anna Meadows	CA-11796
Memorial Sloan-Kettering Cancer Center, New York, NY	Peter Steinherz	—
James Whitcomb Riley Hospital for Children, Indianapolis, IN	Robert Weetman	CA-13809
University of Utah Medical Center, Salt Lake City	Richard O'Brien	CA-10198
Strong Memorial Hospital, Rochester, NY	Harvey Cohen	CA-11174
University of British Columbia, Vancouver, Canada	Mavis Teasdale	CA-29013
Children's Hospital Medical Center, Cincinnati, OH	Beatrice Lampkin	CA-26126
Harbor/UCLA and Miller Children's Medical Center, Torrance and Long Beach, CA	Jerry Finklestein	CA-14560
University of California Medical Center, Los Angeles	Stephen Feig	CA-27678

APPENDIX

Principal Investigators of the Childrens Cancer Study Group (cont'd)

Institution	*Investigator*	*Grant No.*
University of Iowa Hospitals and Clinics, Iowa City	Raymond Tannous	CA-29314
Children's Hospital of Denver, CO	David Tubergen	CA-28851
Mayo Clinic, Rochester, MN	Gerald Gilchrist	CA-28882
Izaak Walton Killam Hospital for Children, Halifax, Nova Scotia, Canada	Allan Pyesmany	—

REFERENCES

1. REAMAN G, ZELTZER P, BLEYER WA, ET AL. Acute lymphoblastic leukemia in infants less than one year of age: a cumulative experience of the Childrens Cancer Study Group. J Clin Oncol 3:1513–1521, 1985.
2. CRIST W, PULLEN J, BOYETT J, ET AL. Clinical and biologic features predict a poor prognosis in acute lymphoid leukemias in infants: a Pediatric Oncology Group study. Blood 67:135–140, 1986.
3. ABE R, RYAN D, CECALUPO A, ET AL. Cytogenetic findings in congenital leukemia: case report and review of the literature. Cancer Genet Cytogenet 9:139–144, 1983.
4. ARTHUR DL, BLOOMFIELD CD, LINDQUIST LL, ET AL. Translocation 4;11 in acute lymphoblastic leukemia: clinical characteristics and prognostic significance. Blood 59:96–99, 1982.
5. STEINHERZ P, GAYNON P, MILLER D, ET AL. Improved disease-free survival of children with acute lymphoblastic leukemia at high risk for early relapse with the New York regimen—a new intensive therapy protocol: a report from the Childrens Cancer Study Group. J Clin Oncol 4:744–752, 1986.
6. WOODS WG, O'LEARY M, and NESBIT ME. Life-threatening neuropathy and hepatotoxicity in infants during induction therapy for acute lymphoblastic leukemia. J Pediatr 98:642–645, 1981.
7. MILLER DR, LEIKIN S, ALBO V, ET AL. Prognostic importance of morphology (FAB classification) in childhood acute lymphoblastic leukemia (ALL). Br J Haematol 48:199–206, 1981.
8. KAPLAN EL, and MEIER P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481, 1958.
9. PETO R, PIKE M, ARMITAGE P, ET AL. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 35:1–39, 1977.

Pediatric Phase I Trial of Carboplatin: A Childrens Cancer Study Group Report[1,2]

Paul S. Gaynon,[3] Lawrence J. Ettinger,[4] Donald Moel,[5] Stuart E. Siegel,[6,7] Edward S. Baum,[5] William Krivit,[8] and G. Denman Hammond[7,8]*

Carboplatin is one of a series of cisplatin analogs now undergoing clinical investigation. Phase I and II trials in adults demonstrate activity in a number of human cancers and less toxicity than might be expected with the parent compound. This phase I trial was undertaken to establish the maximum tolerated dose and the recommended phase II dose in children treated by a 1-hour iv infusion every 4 weeks. Twenty-nine patients with recurrent or progressive tumor were entered in this study at the Children's Hospital of Los Angeles and Children's Memorial Hospital in Chicago between April 12, 1983, and November 27, 1984. Beginning with a dose of 350 mg/m^2 (about 80% of the adult phase II dose), we escalated the dose in groups of patients to 670 mg/m^2; dose-limiting myelosuppression was encountered at this dose. Fifty-seven infusions are at least partially evaluable for toxicity. Asymptomatic hypomagnesemia, hypocalcemia, and ototoxicity were observed infrequently, and nausea and vomiting were mild. One patient with a mixed glioma of the posterior fossa achieved a good partial response lasting 9 months. Stable disease for ≥ 6 months was observed in three patients: one each with ependymoma, brain stem glioma, and spinal cord astrocytoma. The recommended pediatric phase II dose is 560 mg/m^2 given as a 1-hour iv infusion every 4 weeks. [Cancer Treat Rep 71:1039–1042, 1987]

Carboplatin (1–6) is one of a series of analogs of cisplatin, a valuable antitumor agent whose utility is limited by pronounced nonhematologic toxicity (7). Carboplatin is active against several malignant cell lines included in the National Cancer Institute's Tumor Cell Panel. Compared to cisplatin, its low nephrotoxicity and emetogenicity in animal trials led to phase I and II trials in adults (8–15). These studies have demonstrated activity in a variety of human malignancies and have confirmed predictions of decreased nephrotoxicity and emetogenicity. Dose-limiting toxicity has been myelosuppression, especially thrombocytopenia.

Since children may tolerate chemotherapeutic agents differently from adults (16), this study was undertaken to determine the maximum tolerated dose (MTD) and recommended phase II dose for children. Carboplatin was administered as a 1-hour iv infusion every 4 weeks.

MATERIALS AND METHODS

Eligibility Criteria

Patients < 21 years of age with pathological confirmation of malignancy and recurrence or progression of disease despite prior therapy were eligible for the study. Histological confirmation was not required for brain stem tumors. An estimated life expectancy of 8 weeks was required. Patients without bone marrow involvement by tumor were required to have an absolute neutrophil count ≥ 1000/μl and a platelet count ≥ 100,000/μl. Patients with serious infections were excluded from the study. Adequate liver function (bilirubin < 2.0 mg/dl) and renal function (normal for age) were required. Patients with pre-existing high-frequency hearing loss (> 20 dB at ≥ 4 kHz) were excluded. In the absence of both obvious disease pro-

[1] Received Jan 20, 1987; revised July 21, 1987; accepted July 30, 1987.
[2] Supported by Public Health Service grants (CA) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. *See* Appendix. Also supported by the Deborah Goldfine-Reva Smilgoff Memorial Club.
[3] Wyler Children's Hospital and the University of Chicago, IL.
[4] University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, New Brunswick.
[5] Children's Memorial Hospital and Northwestern University, Chicago, IL.
[6] Children's Hospital of Los Angeles, CA.
[7] University of Southern California School of Medicine, Los Angeles.
[8] Variety Club Children's Hospital and the University of Minnesota, Minneapolis.
* *Reprint requests to:* Childrens Cancer Study Group, 199 N Lake Ave, Third Floor, Pasadena, CA 91101.

gression and complete recovery from the toxic effects of prior therapy, patients were excluded if they had received chemotherapy or x-ray therapy in the preceding 4 weeks. Signed informed consent indicating the investigational nature of the study was obtained in accordance with federal and institutional guidelines.

Drug Formulation and Administration

Carboplatin was supplied by the National Cancer Institute in amber vials containing 150 mg each of carboplatin and mannitol as a lyophilized powder. The drug was reconstituted with 9.8 ml of sterile water to a concentration of 15 mg/ml and administered in 5% dextrose in water (300 ml/m^2) as an iv infusion over 1 hour. Drug administration was repeated every 4 weeks. Neither routine antiemetic therapy nor vigorous postinfusion diuresis was employed.

The starting dose was 350 mg/m^2, approximately 80% of the MTD reported from trials in adults (8,12). The dose was escalated initially by 20% of the starting dose and later by 20% of the previous dose in sequential groups of patients. At least three patients were evaluated at each level until grade 4 toxicity was encountered. An additional five patients were assigned to the penultimate level, and as no "unacceptable" toxicity was encountered, this dose was considered to be the MTD. The dose was not escalated for any individual patient.

Patient Monitoring During Study

An interval history, physical examination, and audiogram were required prior to each course of therapy and at removal from the study. A cbc including differential and platelet counts, SGPT, and alkaline phosphatase were obtained weekly; urinalysis and BUN, creatinine, uric acid, serum calcium, and serum magnesium were obtained at baseline, 24 hours after infusion, and weekly thereafter.

Studies to determine tumor response were performed every 4–8 weeks or if signs or symptoms of disease progression developed. A complete response was defined as the disappearance of all known disease without appearance of any new lesion. A partial response was defined as a $> 50\%$ decrease in the product of the largest perpendicular diameters of every measurable lesion, without the appearance of any new lesion. Stable disease was defined as a $< 25\%$ increase in the product of the largest perpendicular diameters of any measurable lesion, without the appearance of any new lesion. Disease progression was defined as a $\geq 25\%$ increase in the product of the largest perpendicular diameters of any measurable lesion, appearance of any new lesion, or worsening of signs or symptoms related to progression of tumor. Complete or partial response or stable disease in patients with brain tumors required, in addition, stable or decreased neurological findings and a stable or decreased steroid dose. The toxicity rating scale of the Childrens Cancer Study Group (CCSG) was utilized in this study; grade 3 or 4 toxicity was considered to be significant. Subsequent infusions of carboplatin were delayed until pre-existing grade 3 or 4 toxicity had resolved.

All of these studies were repeated when a patient was removed from the study. Patients received at least two infusions in the absence of unacceptable toxicity or clearly progressive disease.

RESULTS

Patient Characteristics

Between April 12, 1983, and November 27, 1984, 29 patients were entered in the study at Children's Memorial Hospital in Chicago and Children's Hospital of Los Angeles. Seven patients were female and 22 were male, ranging in age from 2 to 15 years (median, 7). Histological diagnosis is available for all but three patients, who had brain stem tumors. The spectrum of diagnoses is shown in table 1. All patients had recurrent or progressive disease despite one to four previous therapeutic attempts (median, one).

Patients received between one and eight infusions (median, two). Fifty-seven of 66 infusions (86%) were at least partially evaluable for toxicity. Three patients died of disease progression prior to completion of the 4-week observation period. Three, four, five, ten, and seven patients were assigned to receive 350, 420, 490, 560, and 670 mg/m^2, respectively. Two patients each received two infusions at 560 mg/m^2 after an initial infusion at 670 mg/m^2. Data are not available for two of the infusions.

Toxicity

Toxic effects are shown in table 2. Standard CCSG criteria were utilized when available.

Nausea and vomiting were generally mild. Only two patients had more than two episodes of vomiting with any one infusion.

Fifty infusions among 23 patients were evaluable for hearing loss. Baseline audiograms were normal, and serial studies were obtained and reported. Three patients showed minimal (grade 1+; 20–39 dB) high-frequency ($\geq$ 4 kHz) hearing loss (two at 560 mg/m^2 and

TABLE 1.—Diagnoses of patients in study

Diagnosis	No. of patients
Ependymoma	5
Brain stem tumor	5
Acute lymphoblastic leukemia	3
Osteogenic sarcoma	3
Astrocytoma	2
Ewing's sarcoma	2
Glioma	2
Neuroblastoma	2
Wilms' tumor	2
Primitive neuroectodermal tumor	1
Alveolar rhabdomyosarcoma	1
Undifferentiated malignant tumor	1

TABLE 2.—Toxic effects

Dose (mg/m^2)	No. of infusions		Grade			
	Total	Evaluable	0/1+	2+	3+	4+
			Nausea and vomiting			
350	10	10	4	6		
420	8	4	2	2		
490	8	6	4	2		
560	21	14	7	6	1	
670	12	8	0	6	2	
			High-frequency hearing loss			
350	10	10	10			
420	8	4	4			
490	8	7	6	1		
560	21	20	19	1		
670	12	9	9			
			Hypomagnesemia			
350	10	8	8			
420	8	7	6	1		
490	8	8	8			
560	21	21	20		1	
670	12	10	9	1		
			Neutropenia			
350	10	10	9	1		
420	8	6	3	3		
490	8	6	3	3		
560	21	16	7	4	5	
670	12	10	1	1	5	3
			Thrombocytopenia			
350	10	10	10			
420	8	8	5	2	1	
490	8	6	5	1		
560	21	19	12	3	3	1
670	12	10	2	2	4	2

one at 670 mg/m^2). Two patients showed moderate (grade 2+; 40–54 dB) loss (one at 490 mg/m^2 and one at 560 mg/m^2). An 8-year-old child with an ependymoma and previous brain irradiation developed a moderate deficit following two infusions at a dose of 490 mg/m^2. Only slight improvement was evident 2 months after cessation of carboplatin. At 560 mg/m^2, a 15-year-old adolescent with osteosarcoma and previous exposure to cisplatin developed moderate high-frequency hearing loss. No patient was symptomatic.

Serum BUN and creatinine were closely monitored for each infusion. No abnormalities were observed, with the exception of one patient who was moribund secondary to tumor progression and was dehydrated. Urinary protein losses were never > 128 mg/24 hours.

Three instances of asymptomatic hypomagnesemia were noted. One patient received additional carboplatin without incident. At a dose of 670 mg/m^2, one patient had asymptomatic minimal hypocalcemia with each of two infusions (grade 1+); asymptomatic hypomagnesemia developed after the second infusion.

Patients with leukemia or with bone marrow invasion by tumor were not evaluable for myelosuppression. Myelosuppression was dose limiting in this study. At a dose of 560 mg/m^2, five of 16 infusions were associated with neutropenia: an absolute neutrophil count $< 1000/\mu l$ (three of ten patients). At 670 mg/m^2, eight of ten infusions had similar toxicity, affecting all seven patients receiving the infusions. The lowest absolute neutrophil count was $252/\mu l$ and required 1 week for recovery. The difference in episodes per infusion is of borderline statistical significance by Fisher's exact test ($P = 0.041$).

Maximal myelosuppression occurred about 21 days after infusion. Blood cell counts generally recovered by Day 28.

At a dose of 560 mg/m^2, one infusion resulted in a platelet count nadir of $23,000/\mu l$, which required 1 week for recovery. Seven of 19 infusions were associated with thrombocytopenia: a platelet count nadir $< 75,000/\mu l$ (three of ten patients). At 670 mg/m^2, eight of ten infusions resulted in thrombocytopenia (six of seven patients). The lowest platelet count was $2000/\mu l$ and required 2 weeks for recovery. The difference in episodes per infusion is of borderline statistical significance by Fisher's exact test ($P = 0.05$).

Fever to 38.8°C following infusion, generalized pruritus without rash, and hives were each observed in one patient. No patient had paresthesias. Following carboplatin, one patient developed atrial flutter, and an echocardiogram showed pericardial metastases. One patient had mild, transient elevation of SGPT.

Therapeutic Activity

One patient with a mixed glioma of the posterior fossa achieved partial response with 75% decrease in tumor area, as evidenced by computerized tomography scan after two courses of therapy at a dose of 670 mg/m^2. The response lasted 9 months. Two patients with brain stem glioma had stable disease for 4 months at 420 mg/m^2 and 6 months at 350 mg/m^2. One patient with an ependymoma and one with spinal cord astrocytoma had stable disease for 10 and 7 months, respectively, at 560 mg/m^2. All five patients had been treated with only one protocol prior to this study, and none had previously received cisplatin.

DISCUSSION

Carboplatin is an analog of cisplatin that lacks the severe emetogenicity, ototoxicity, and nephrotoxicity of the parent compound. With carboplatin, unlike cisplatin, transient myelosuppression is dose limiting. Dose-limiting toxicity was encountered at 670 mg/m^2. The recommended dose for pediatric phase II trials is 560 mg/m^2 iv over 1 hour every 4 weeks. No intermediate dose was studied.

The recommended dose for solid tumor phase II trials in adults, utilizing the same schedule of administration every 4 weeks, is 300–450 mg/m^2 (6–10,12,13,17). In our pediatric trials, unlike the adult trials, ototoxicity, hypomagnesemia, and hypocalcemia were noted, although infrequently and without symptoms. With cisplatin, ototoxicity has been noted to be more severe in children

than in adults (18). Joss et al (19) observed proteinuria in adults; this was not observed in our study, which included only children.

The durable partial response in the patient with glioma and stable disease for $\geq$ 6 months in three other children with brain tumors are encouraging. Should activity be demonstrated in ongoing adult and pediatric phase II trials, a randomized comparison of carboplatin and cisplatin as components of combination chemotherapy may be warranted. Both agents should be tested at isotoxic doses, as response to either may well be dose dependent (17,20). The dose-limiting toxicity of carboplatin (ie, reversible myelosuppression at 560 mg/m^2) appears more *acceptable* than the dose-limiting toxicity of cisplatin (ie, severe nausea and vomiting, irreversible ototoxicity, and nephrotoxicity at 90 mg/m^2). The molar dose of carboplatin is 4.5 times greater. Questions with regard to cumulative myelosuppression must await further clinical experience.

Both the Pediatric Oncology Group and the CCSG are currently conducting phase II trials utilizing the dose and schedule tested here.

APPENDIX

Principal Investigators of the Childrens Cancer Study Group

Institution	*Investigator*	*Grant No.*
Group Operations Office, University of Southern California Comprehensive Cancer Center, Los Angeles	Denman Hammond John Weiner Harland Sather Richard Sposto Mark Krailo Jonathan Buckley	CA-13539
Children's Memorial Hospital, Chicago, IL	Edward Baum	CA-07431
Children's Hospital of Los Angeles, CA	Jorge Ortega	CA-02649

REFERENCES

1. Clinical Brochure: CBDCA (NSC-241240). Bethesda, MD, National Cancer Institute, Sept 1981.
2. HARRAP KR, JONES M, WILKENSON CR, ET AL. Antitumor, toxic, and biochemical properties of cisplatin and eight other platinum complexes. *In* Cisplatinum: Current Concepts and New Concepts (Prestakyo AW, Crooke ST, and Carter SK, eds). New York, Academic Press, 1980, pp 193–212.
3. WOLPERT-DEFILIPPES MK. Antitumor effect of cisplatin analogues. *In* Cisplatinum: Current Concepts and New Concepts (Prestakyo AW, Crooke ST, and Carter SK, eds). New York, Academic Press, 1980, pp 183–192.
4. ROSE WC, SCHURIG JE, HUFTALEN JB, ET AL. Antitumor activity and toxicity of cisplatin analogs. Cancer Treat Rep 66:135–146, 1982.
5. LEE HL, CANETTA R, ISSELL BF, ET AL. New platinum complexes in clinical trials. Cancer Treat Rev 10:39–51, 1983.
6. WHELAN JE, URBANEK MA, and LIAO JT. A toxicologic evaluation of diammine [1,1-cyclobutane dicarboxylato (2-)*O*,*O*']-(SP-4-2) platinum (CBDCA), in CDF1 mice. Proc Am Assoc Cancer Res 23:170, 1982.
7. LOEHRER PJ, and EINHORN LH. Cisplatin. Ann Intern Med 100:704–713, 1984.
8. CALVERT AH, NEWELL DR, SIDDIK ZH, ET AL. Early clinical studies with *cis*-diammine-1,1-cyclobutane dicarboxylate platinum II. Cancer Chemother Pharmacol 9:140–147, 1982.
9. EVANS BD, RAJU KS, CALVERT AH, ET AL. Phase II study of JM8, a new platinum analog, in advanced ovarian carcinoma. Cancer Treat Rep 67:997–1000, 1983.
10. CURT GA, GRYGIEL JJ, WEISS R, ET AL. A phase I and pharmacokinetic study of CBDCA (NSC-241240). Proc ASCO 2:21, 1983.
11. EGORIN MJ, VAN ECHO DA, WHITACRE MY, ET AL. Phase I study and pharmacokinetics of carboplatin (CBDCA) (NSC-241240). Proc ASCO 2:28, 1983.
12. LASSUS M, OHNUMA T, LEYVRAZ S, ET AL. A phase I study of CBDCA (carboplatin). Proc ASCO 2:37, 1983.
13. KOELLER JM, EARHART RH, DAVIS TE, ET AL. Phase I trial of carboplatin (NSC 241240) by bolus injection. Proc Am Assoc Cancer Res 24:162, 1983.
14. KAPLAN S, JOSS R, SESSA C, ET AL. Phase I trials of *cis*-diammine-1,1-cyclobutane dicarboxylate platinum II (CBDCA) in solid tumors. Proc Am Assoc Cancer Res 24:132, 1983.
15. OHNUMA T, LEYVRAZ S, COFFEY V, ET AL. Carboplatin: activity in patients with head and neck (H&N), renal cell (RC), and ovarian carcinomas. Proc Am Assoc Cancer Res 25:179, 1984.
16. MARSONI S, UNGERLEIDER RS, HURSON SB, ET AL. Tolerance to antineoplastic agents in children and adults. Cancer Treat Rep 69:1263–1269, 1985.
17. SAMSON MK, RIVKIN SE, JONES SE, ET AL. Dose-response and dose-survival advantage for high versus low dose cisplatin combined with vinblastine and bleomycin in disseminated testicular cancer. Cancer 53:1029–1035, 1984.
18. MCHANEY VA, THIBADOREX G, HAYES FA, ET AL. Hearing loss in children receiving cisplatin chemotherapy. J Pediatr 102:314–317, 1983.
19. JOSS RA, KAPLAN S, GOLDHIRSCH A, ET AL. A phase I trial of *cis*-diammine-1,1-cyclobutane dicarboxylate platinum—every five week schedule. Invest New Drugs 2:297–304, 1984.
20. OZOLS RF, CORDEN BJ, JACOB J, ET AL. High dose cisplatin in hypertonic saline. Ann Intern Med 100:19–24, 1984.

Pharmacokinetics of Continuous-Infusion High-Dose Thiotepa[1,2]

William D. Henner,* Thomas C. Shea, Eileen A. Furlong, Mary D. Flaherty, J. Paul Eder, Anthony Elias, Colin Begg, and Karen Antman[3]

The pharmacokinetics of thiotepa administered as a continuous infusion over 4 days have been studied in 18 patients receiving high-dose thiotepa, cyclophosphamide, and autologous bone marrow reinfusion as treatment for advanced neoplasms. Patients received cyclophosphamide at a total dose of 6 g/m^2 and thiotepa at a total dose of 180–900 mg/m^2 over the 4-day infusion. Samples of plasma were obtained during and following infusion, and the plasma concentration of thiotepa was determined by the method of Egorin et al. For many patients (72%), peak concentrations of plasma thiotepa were achieved during the initial 24 hours of infusion and then declined an average of 29% by the end of the 96-hour infusion. The average total systemic clearance of thiotepa was 16.7 ± 7.4 (SD) L/m^2/hour [or 420 ± 162 (SD) ml/kg/hr]. An inverse correlation between the average total systemic clearance and the dose of thiotepa was observed ($P < 0.01$). [Cancer Treat Rep 71:1043–1047, 1987]

The use of high-dose chemotherapy with either autologous or allogeneic bone marrow transplantation has recently been increasing in the treatment of leukemias, lymphomas, and solid tumors (1–6). Many of these programs utilize therapeutic regimens of high doses of alkylating agents prior to transplantation.

Thiotepa, an alkylating agent used clinically for > 30 years (7–9), is a component of current regimens for breast cancer (10,11), intravesicular therapy of superficial bladder cancer (12,13), and intrathecal therapy of meningeal neoplasias (14–17). Because of its broad activity and relative lack of nonhematologic toxicity at conventional doses, thiotepa, either as a single agent (18,19) or in combination with high-dose cyclophosphamide (20), has been incorporated into high-dose chemotherapy regimens using autologous bone marrow transplantation.

Renewed interest in the optimal use of thiotepa led to the development of sensitive and specific gas chromatographic methods for quantitation of thiotepa in biologic fluids (21–25) after administration as an iv bolus at both standard doses (26) and transplant doses (18,20,27) or following intrathecal treatment (21).

The current phase I study utilized a constant dose of cyclophosphamide and escalating doses of thiotepa. The combination of thiotepa and cyclophosphamide was selected for its ability to produce supra-additive cytotoxicity in cultured human tumor cells and in animal tumor models (28). In this study, both drugs were administered by continuous infusion, in an attempt to improve the therapeutic index, particularly in low growth-fraction tumors such as breast carcinoma. Thiotepa was administered at high doses (180–900 mg/m^2) by continuous iv infusion over a 4-day period, with concurrent continuous infusion of cyclophosphamide (6 g/m^2). Chemotherapy was followed 3 days later by reinfusion of cryopreserved autologous bone marrow. The pharmacokinetic parameters of thiotepa administered on this schedule are reported here. The antitumor responses and toxicity observed with this treatment will be the subject of a separate report.

MATERIALS AND METHODS

Materials.—Thiotepa was donated by Lederle Laboratories (Wayne, NJ). Diphenylamine was obtained from Sigma Chemical Co. (St. Louis, MO), and ethylacetate was high-performance liquid chromatography grade.

Patient selection and treatment.—Blood samples for this study were obtained from a series of 21 patients entered in a phase I study of high-dose thiotepa and cyclophosphamide, with autologous bone marrow reinfusion. Cyclophosphamide and thiotepa were adminis-

[1] Received Feb 19, 1987; revised June 29, 1987; accepted July 30, 1987.
[2] Supported by Public Health Service grant CA-38493 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. W. D. Henner is the recipient of a Leukemia Society of America Scholar Award. T. C. Shea is the recipient of a fellowship award from the Pharmaceutical Manufacturers Association Foundation.

[3] Divisions of Cancer Pharmacology (*W. D. Henner, T. C. Shea, E. A. Furlong,* and *M. D. Flaherty*), Medicine (*J. P. Eder, A. Elias,* and *K. Antman*), and Biostatistics (*C. Begg*), Dana-Farber Cancer Institute, Boston, MA.
* *Reprint requests to:* William D. Henner, MD, PhD, Division of Cancer Pharmacology, Dana-Farber Cancer Institute, 44 Binney St, RM JF817, Boston, MA 02115.

tered concurrently as 4-day continuous iv infusions via indwelling central venous catheters. The total dose of cyclophosphamide administered was 6 g/m^2 for all patients, and the total dose of thiotepa was 180–900 mg/m^2. Blood samples were not obtained for drug level monitoring from three of the 21 patients treated in this study; these patients are therefore not included in this report. Pretreatment evaluation included determination of creatinine clearance by 24-hour collection of urine and by serum collection. All patients had serum creatinine levels < 1.5 mg/100 ml and normal bilirubin, transaminase, and LDH levels. Cardiac function was normal in all patients as assessed by physical examination and ECG. All institutional review requirements, including informed consent, were fulfilled.

Administration of drug.—Thiotepa was obtained as a sterile powder from Lederle Laboratories in vials containing 15 mg of thiotepa, 80 mg of NaCl, and 50 mg of $NaHCO_3$. Each vial was reconstituted with 1.5 ml of sterile water for injection to yield a drug concentration of 10 mg/ml in an isotonic solution of approximately pH 7.6. Fresh solutions for infusion were prepared every 24 hours.

Sample collection, storage, and analysis.—Blood samples (10 ml) were collected in EDTA-containing tubes prior to initiation of treatment and at 12-hour intervals during and following the end of infusion. Plasma was separated by centrifugation and stored at −20°C until analysis. For some patients, additional samples of plasma were obtained at the end of infusion and at 1-hour intervals after infusion for up to 3 hours.

Assay of plasma thiotepa.—Plasma thiotepa levels were determined by minor modification of the gas chromatographic method described by Egorin and coworkers (23). Plasma samples were thawed and extracted with three volumes of ethylacetate containing 5 μM diphenylamine. A portion of the ethylacetate phase (1–2 μl) was injected into an HP 5890A gas chromatograph (Hewlett-Packard Co, Palo Alto, CA) equipped with a split-splitless injector set with a split ratio of 1.4. The column used was an HP 17 530-μm (0.53 mm × 10 m) wide-bore capillary column (Hewlett-Packard Co). Column and injection-port ovens were set at 170°C and 230°C, respectively. The helium flow rate was 20.5 ml/minute. Detection was achieved using a nitrogen-phosphorus detector with a baseline current of 30–50 pA to the bead; the detector oven was set at 230°C. Hydrogen-flow and airflow rates were 3.5 and 110 ml/minute, respectively. Peak areas were determined using a 3392A integrator (Hewlett-Packard Co). Thiotepa concentrations were determined by peak-area ratios using diphenylamine as the internal standard. The limit of detection of plasma thiotepa was 0.02 μM.

Calculation of pharmacokinetic parameters and statistical analyses.—The area under the drug concentration-time curve (AUC) was calculated by the linear trapezoidal method, and the total systemic clearance (Cl_{ss}) was calculated according to the relationship Cl_{ss} = dose/AUC (29).

Correlation coefficients were calculated between Cl_{ss} and the factors of age, creatinine clearance, and dose, along with the P values for a test of no association. The test for a relationship between gender and Cl_{ss} was computed by a two-sample t test.

RESULTS

Blood samples for thiotepa levels were available from 18 patients treated in this phase I protocol. Patients studied were treated at five dose levels of thiotepa: 180 mg/m^2 (five patients); 360 (five); 500 (two); 720 (three); and 900 (three). All patients concurrently received cyclophosphamide at 6 g/m^2. Patient characteristics of possible relevance to the pharmacokinetics of thiotepa are listed in table 1. All patients had normal cardiac and hepatic functions (as defined in Materials and Methods section) at the time of treatment.

A time course for plasma thiotepa levels during the 4-day infusion period for a patient who received thiotepa at a dose of 720 mg/m^2 is shown in figure 1. Maximum levels of thiotepa were generally achieved within 12–24 hours of the initiation of treatment. Although the infusion rate was held constant, for most patients (72%), the thiotepa levels declined thereafter from the peak by an average of 29% during the 4 days of infusion. On completion of the infusion, thiotepa levels declined rapidly. None of the patients had detectable levels of thiotepa by 36 hours after infusion. To obtain an estimate of the terminal half-life of thiotepa administered on this schedule, we collected plasma samples at the end of the infusion and over the ensuing 3 hours (n = 23 samples) for a subset of the patients (n = 11). The mean half-life of thiotepa for these patients was 2.0 ± 0.9 (SD) hours.

Plasma thiotepa levels in figure 1 are not consistent with any standard one- or two-compartment pharmacokinetic model. For this reason, the drug levels were analyzed in terms of noncompartmental parameters such as Cl_{ss} and peak concentrations achieved. The pharmacokinetic parameters calculated for this group of patients are shown in table 1. Both drug exposure and peak drug concentrations were clearly related to the dose administered (table 1 and fig 2). Peak levels of thiotepa ranged from 0.33 μM for a patient treated with 180 mg/m^2 to 7.2 μM for a patient treated with 900 mg/m^2 (table 1). The AUC ranged from 26.0 μM·hour for a patient treated with 180 mg/m^2 to 590.5 μM·hour for a patient treated with 900 mg/m^2 (fig 2). From the dose and the AUC, the Cl_{ss} for each patient was calculated; it ranged from 8.1 to 36.5 L/m^2/hour (table 1).

In this phase I study, the dose of thiotepa varied over a fivefold range (180–900 mg/m^2). It was important to determine if clearance was related to dose, that is, if there was any evidence for saturation of clearance at high doses. In this series, an inverse relationship was observed between the dose administered and Cl_{ss} (correlation coefficient, −0.56; $P < 0.01$) (fig 3). There was no significant relationship observed between Cl_{ss} and patient gender or age or whether the patient had re-

TABLE 1.—Patient characteristics relevant to thiotepa pharmacokinetics*

Patient No. (n = 18)	Sex	Age (yrs)	Cl_{cr} (L/m²/hr)	Prior chemotherapy	Dose (mg/m²)	Peak (μM)	AUC (μM·hr)	Cl_{tp} (L/m²/hr)
1	M	42	5.81	N	180	0.78	46.2	20.3
2	F	38	4.13	N	180	0.33	26.0	36.5
3	M	43	4.94	N	180	1.5	85.9	11.1
4	F	32	3.71	Y	180	0.64	35.4	26.8
5	F	48	1.07	Y	180	0.54	44.8	21.3
6	F	28	2.13	Y	360	1.6	105.4	18.0
7	M	33	5.69	N	360	1.6	94.0	20.3
8	M	41	3.06	Y	360	2.5	178.6	10.6
9	F	24	4.77	Y	360	2.3	126.0	15.0
10	M	30	5.06	Y	360	0.96	73.6	25.8
12	M	48	3.22	Y	500	2.9	224.8	11.6
13	F	29	4.00	Y	500	2.2	171.3	15.2
15	F	42	4.46	Y	720	5.8	432.3	8.8
16	F	30	5.92	Y	720	4.8	282.2	13.5
17	F	39	3.84	Y	720	4.7	326.3	11.6
19	F	28	4.86	N	900	6.9	456.8	10.5
20	F	34	5.01	Y	900	7.2	590.5	8.1
21	M	34	5.38	Y	900	4.8	308.7	15.5
Total	11 F/7 M			5 N/13 Y				
Mean		35	4.28					16.7 ± 7.4 SD

*M = male and F = female; Cl_{cr} = creatinine clearance; N = no prior chemotherapy; and Y = prior chemotherapy.

ceived prior chemotherapy. However, the age range of patients treated in this study (28–48 yrs) was narrow, and the possibility of altered pharmacokinetics of thiotepa in elderly or pediatric patients cannot be excluded. Also, as expected from the results of other investigators, there is no relationship between renal function (creatinine clearance) and thiotepa clearance.

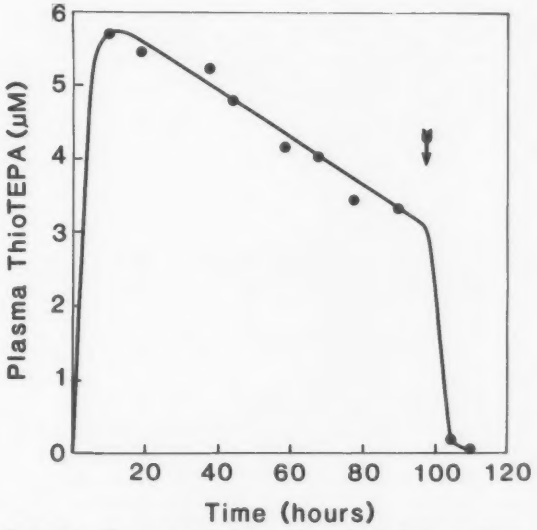

FIGURE 1.—Time course of plasma thiotepa levels during continuous high-dose infusion. Patient 15 received thiotepa at a total dose of 720 mg/m² administered from 0 time to 96 hrs (arrow). At indicated times, blood samples were drawn and plasma thiotepa levels were determined as described in Materials and Methods section.

DISCUSSION

An understanding of the pharmacokinetics of drugs used in high-dose therapy with autologous bone marrow

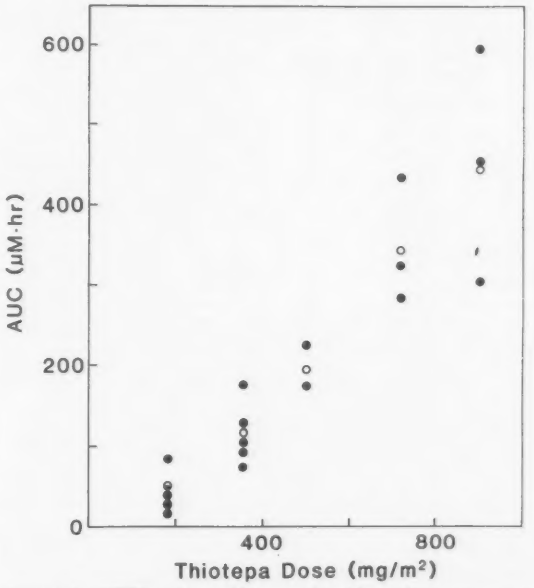

FIGURE 2.—AUC for plasma thiotepa vs dose. From plasma concentrations of thiotepa at various times for each patient, AUC was determined as described in Materials and Methods section. AUC determined for each treatment course is indicated by filled circles and is plotted vs total dose of thiotepa administered for that patient. Mean AUC at each dose level is indicated by open circles.

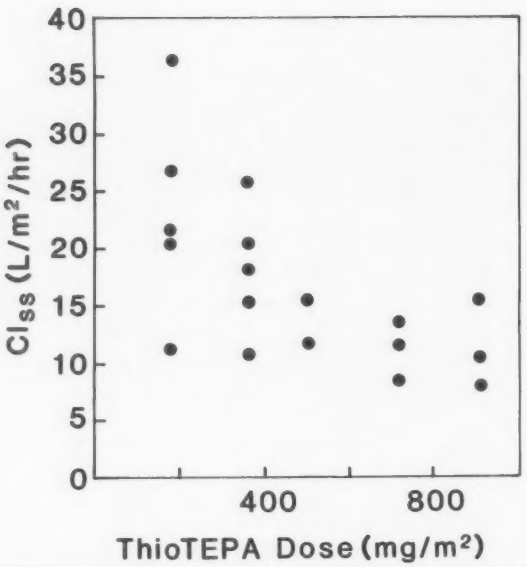

FIGURE 3.—Cl_{ss} of thiotepa vs dose. Cl_{ss} was calculated for each patient as described in Materials and Methods section and plotted vs total dose of thiotepa administered for that patient.

transplantation is important in developing optimal doses and schedules for these regimens and in avoiding the associated life-threatening toxic effects. As such therapy is usually administered only once to a given patient, drug dosage cannot be adjusted on the basis of toxic effects observed in previous courses of therapy. In addition, the pharmacokinetics of a drug given in one schedule can often be used to predict the time course of drug levels for the same drug administered in an alternate dosage or schedule. For high-dose thiotepa given by continuous infusion, the AUC, the corresponding Cl_{ss}, the peak plasma thiotepa levels, and the terminal half-life are approximately those expected from the pharmacokinetics determined by others for thiotepa given at standard dosage or at high doses by iv bolus (20,26,27).

However, the novel schedule and wide dose range utilized in this study have allowed new observations concerning thiotepa kinetics that were not apparent from the low-dose or high-dose bolus studies. First, Cl_{ss} for thiotepa was inversely related to the dose administered in this group of patients. Thiotepa is largely metabolized to tepa and other alkylating metabolites in humans, rather than being excreted as the parent drug (26), suggesting that thiotepa is metabolized by a saturable enzymatic process. Such metabolism is likely to take place at least in part in the liver, as metabolism of thiotepa to more mutagenic species can be effected by liver extracts (30), and tissue distribution studies in mice have also suggested that the liver is an important site of thiotepa metabolism (31).

A second and related observation was a decline in thiotepa plasma levels over the 4 days of infusion. For some of the patients studied (eg, fig 1), the decline was clear-cut. Although the phenomenon was observed in only 72% of the patients and did not reach statistical significance for the group as a whole, the possibility that thiotepa clearance may change over the course of treatment in some patients should be considered in the design of future studies of the pharmacokinetics of this drug. The reason for the apparent increase in clearance of thiotepa during infusion in some patients is not known. However, hypotheses that might be tested in future studies include induction of an enzyme system for metabolism of thiotepa or changes in the volume of distribution of the drug over the course of treatment.

Thiotepa was administered in this study in combination with high-dose cyclophosphamide. There is an overall similarity between the pharmacokinetic parameters for thiotepa in this study and those in studies of thiotepa administered as a single agent (18,29), suggesting that cyclophosphamide does not markedly alter thiotepa clearance. However, it would be important to determine whether the saturation of clearance and the apparent "induction" of clearance observed in this study occur when thiotepa is administered as a single agent.

In summary, the Cl_{ss} of high-dose continuous-infusion thiotepa in humans is similar to the Cl_{ss} when the drug is administered by bolus injection. In addition, the negative correlation between Cl_{ss} and dose indicates that clearance of thiotepa is a saturable process. Observations suggest the possibility that clearance of thiotepa may be inducible in some patients. Further studies to define the processes and sites involved in clearance of thiotepa are under way.

REFERENCES

1. ABRAMS RA, ANDERSON K, ANTMAN K, ET AL. Bone-marrow autotransplantation in man: report of an international cooperative study. Lancet 2:960-962, 1986.
2. PHILLIPS GL, HERZIG RH, LAZARUS HM, ET AL. Treatment of resistant malignant lymphoma with cyclophosphamide, total body irradiation, and transplantation of cryopreserved autologous marrow. N Engl J Med 310:1557-1561, 1984.
3. POSTMUS PE, DE VRIES GE, DE VRIES HG, ET AL. Cyclophosphamide and VP 16-213 with autologous bone marrow transplantation: a dose escalation study. Eur J Cancer Clin Oncol 20:777-782, 1984.
4. VOGLER WR, and WINTON EF. Autologous marrow transplantation: current status and future directions. Prog Clin Cancer 8:45-56, 1982.
5. KAIZER H, and SANTOS GW. Autologous bone marrow transplantation in treatment of leukemia, lymphomas and other cancers. Prog Clin Cancer 8:31-44, 1982.
6. PETERS WP, EDER JP, HENNER WD, ET AL. High-dose combination alkylating agents with autologous bone marrow support: a phase I trial. J Clin Oncol 4:646-654, 1986.
7. SYKES M, KARNOFSKY D, PHILLIPS F, ET AL. Clinical studies of triethylene-phosphoramide and diethylenephosphoramide compounds with nitrogen mustard-like activity. Cancer 6:142-148, 1953.
8. BATEMAN JC. Chemotherapy of solid tumors with triethylenethiophosphoramide. N Engl J Med 252:879-887, 1955.
9. ULTMANN JE, HYMAN GA, CRANDALL C, ET AL. Triethylenethiophosphoramide (thio-TEPA) in the treatment of neoplastic disease. Cancer 10:902-911, 1957.
10. HART RD, PERLOFF M, and HOLLAND JF. One day VATH therapy for advanced breast cancer refractory to prior chemotherapy.

Cancer 48:1522–1527, 1981.
11. PERLOFF M, HART RD, and HOLLAND JF. Vinblastine, Adriamycin, thiotepa and halotestin (VATH): therapy for advanced breast cancer refractory to prior therapy. Cancer 39:1289–1293, 1977.
12. VEENEMA RJ, DEAN AL, JR, USON AC, ET AL. Thiotepa bladder instillations: therapy and prophylaxis for superficial bladder tumors. J Urol 101:711–715, 1969.
13. MASTERS JR. Intravesical chemotherapy. Lancet 1:740, 1986.
14. TRUMP DL, GROSSMAN SA, THOMPSON G, ET AL. Treatment of neoplastic meningitis with intraventricular thiotepa and methotrexate. Cancer Treat Rep 66:1549–1551, 1982.
15. GUTIN PH, LEVI JA, WIERNIK PH, ET AL. Treatment of malignant meningeal disease with intrathecal thioTEPA: a phase II study. Cancer Treat Rep 61:885–887, 1977.
16. GUTIN PH, WEISS HD, WIERNIK PH, ET AL. Intrathecal *N,N′,N″*-triethylenethiophosphoramide [thio-TEPA (NSC 6396)] in the treatment of malignant meningeal disease: phase I–II study. Cancer 38:1471–1475, 1976.
17. GIANNONE L, GRECO FA, and HAINSWORTH JD. Combination intraventricular chemotherapy for meningeal neoplasia. J Clin Oncol 4:68–73, 1986.
18. BROWN R, HERZIG R, FAY J, ET AL. A phase I–II study of high-dose *N,N′,N″*-triethylenethiophosphoramide (thiotepa) and autologous marrow transplantation (AMT) for refractory malignancies. Proc ASCO 5:494, 1986.
19. HERZIG R, BROWN R, FAY J, ET AL. High-dose *N,N′,N″*-triethylenethiophosphoramide (thio-tepa) and autologous marrow transplantation (AMT) for metastatic malignant melanoma (MMM). Proc ASCO 5:489, 1986.
20. WILLIAMS S, BITRAN J, RATAIN M, ET AL. A phase I–II study of bialkylator chemotherapy (BACT) with high-dose thiotepa (TT) and Cytoxan and autologous bone marrow reinfusion in patients with refractory lymphoma and disseminated carcinoma. Proc ASCO 5:549, 1986.
21. GROCHOW L, GROSSMAN S, GARRETT S, ET AL. Pharmacokinetics of intraventricular thioTEPA in patients with meningeal carcinomatosis. Proc ASCO 1:19, 1982.
22. COHEN BE, EGORIN MJ, NAYAR MSB, ET AL. Effects of pH and temperature on the stability and decomposition of *N,N′,N″*-triethylenethiophosphoramide in urine and buffer. Cancer Res 44: 4312–4316, 1984.
23. EGORIN MJ, COHEN BE, KOHLHEPP EA, ET AL. Gas-liquid chromatographic analysis of *N,N′,N″*-triethylenethiophosphoramide and *N,N′,N″*-triethylenephosphoramide in biological samples. J Chromatogr 343:196–202, 1985.
24. HAGEN B, WALSETH F, WALSTAD RA, ET AL. Gas chromatographic assay of triethylenethiophosphoramide in serum and urine. J Chromatogr 345:173–177, 1985.
25. MCDERMOTT BJ, DOUBLE JA, BIBBY MC, ET AL. Gas chromatographic analysis of triethylenethiophosphoramide and triethylenephosphoramide in biological specimens. J Chromatogr 338:335–345, 1985.
26. COHEN BE, EGORIN MJ, KOHLHEPP EA, ET AL. Human plasma pharmacokinetics and urinary excretion of thiotepa and its metabolites. Cancer Treat Rep 70:859–864, 1986.
27. LAZARUS HM, REED MD, SPITZER TR, ET AL. High-dose iv thiotepa and cryopreserved autologous bone marrow transplantation for therapy of refractory cancer. Cancer Treat Rep 71:689–695, 1987.
28. TEICHER BA, GENEREUX CA, CUCCHI CA, ET AL. Combination treatment with thioTEPA and Cytoxan can produce supra-additive tumor cell killing in vitro and in vivo. Proc Am Assoc Cancer Res 28:1654, 1987.
29. GIBALDI M, and PERRIER D. Pharmacokinetics. New York, Marcel Dekker, 1982.
30. BREAU AP, FIELD L, and MITCHELL WM. Thiono compounds. 4. In vitro mutagenic and antineoplastic activity of TEPA and thio-TEPA. Cell Biol Toxicol 1:21–30, 1984.
31. EGORIN MJ, AKMAN SR, and GUTIERREZ PL. Plasma pharmacokinetics and tissue distribution of thiotepa in mice. Cancer Treat Rep 68:1265–1268, 1984.

Carboplatin or Iproplatin in Advanced Non-Small Cell Lung Cancer: A Cancer and Leukemia Group B Study[1,2]

Harvey Kreisman,[3,*] Sandra Ginsberg,[4] Kathleen J. Propert,[5] Frederick Richards,[6] Stephen Graziano,[4] and Mark Green[7,8]

The effect of the cisplatin analogs carboplatin (CBDCA) or iproplatin (CHIP) was evaluated in patients with extensive non-small cell lung cancer. The randomized phase II design was used to achieve balance between patient groups and comparison of response rates was not a primary objective of the study. CBDCA (400 mg/m^2 iv) or CHIP (270 mg/m^2 iv) was administered every 4 weeks until relapse of disease. Overall, 11 of 70 patients (16%; 95% confidence interval: 7%–25%) responded to CBDCA and five of 71 patients (7%; 95% confidence interval: 1%–13%) responded to CHIP. There were two complete responses to CHIP and none to CBDCA. The most frequent severe or life-threatening toxic effects were thrombocytopenia and leukopenia. Median survival for patients receiving CBDCA was 6.5 months; for those on CHIP it was 5.0 months ($P = 0.59$). CBDCA is probably active in patients with non-small cell lung cancer whereas CHIP has limited activity. Further evaluation of CBDCA as part of combination chemotherapy for non-small cell lung cancer is warranted. [Cancer Treat Rep 71:1049–1052, 1987]

Metastatic non-small cell lung cancer (NSCLC) is a rapidly progressive and ultimately fatal disease. Although chemotherapy is used to treat this tumor, response rates are poor and treated patients may not have a prolongation of survival.

In phase I trials, the cisplatin analogs iproplatin (CHIP) and carboplatin (CBDCA) have been less nephrotoxic and emetogenic than the parent compound. These analogs are active in small cell lung cancer (1) and in ovarian carcinoma (2). This report evaluates a phase II Cancer and Leukemia Group B (CALGB) trial of two cisplatin analogs, CBDCA and CHIP, in patients with advanced NSCLC.

METHODS

The standard CALGB randomized phase II study design for advanced NSCLC was employed. The primary intent was to determine, but not necessarily to compare, the response rates to new agents in NSCLC. Patients were stratified by histologic type (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) and randomly assigned to treatment with either CBDCA (400 mg/m^2 by iv bolus) or CHIP (270 mg/m^2 iv over 30 minutes) every 28 days. There was no pre- or post-treatment hydration administered. Drug doses were modified on the basis of day-of-treatment hematologic

[1] Received Feb 27, 1987; revised July 27, 1987; accepted Aug 3, 1987.

[2] This study was conducted by the Cancer and Leukemia Group B and was supported by Public Health Service grants (CA) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and by a grant from the T. J. Martell Foundation. The following members participated in this study: Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC (*R. Cooper*, CA-03927); Upstate Medical Center at Syracuse, NY (*A. Gottlieb*, CA-21060); Rhode Island Hospital, Providence (*L. Leone*, CA-08025); Dartmouth-Hitchcock Medical Center, Hanover, NH (*G. Cornwell*, CA-04326); McGill Cancer Center, Montreal, Canada (*J. L. Hutchison*, CA-31809); University of California at San Diego (*M. Green*, CA-11789); University of Missouri, Columbia (*M. Perry*, CA-12046); Long Island Jewish Medical Center, New Hyde Park, NY (*K. Rai*, CA-11028); University of Minnesota, Minneapolis (*B. Peterson*, CA-16450); Walter Reed Army Medical Center, Washington, DC (*R. Weiss*, CA-26806); West Virginia University Medical Center, Morgantown (*P. Raich*, CA-28562); Massachusetts General Hospital, Boston (*R. Carey*, CA-12449); Dana-Farber Cancer Institute, Boston, MA (*G. Canellos*, CA-32291); Cornell Medical Center, New York, NY (*R. R. Silver*, CA-07968); Wilmington Medical Center, DE (*I. Berkowitz*, CA-37041); Columbia University, New York, NY (*R. R. Ellison*, CA-12011); Central Massachusetts Oncology Group (*M. Costanza*, CA-37135); and Harvard School of Public Health, Boston, MA (*J. R. Anderson*, CA-33601).

[3] McGill Cancer Center and The Sir Mortimer B. Davis-Jewish General Hospital, Montreal, Quebec, Canada.

[4] Upstate Medical Center at Syracuse, NY.

[5] Department of Biostatistics, Harvard School of Public Health, Boston, MA.

[6] Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC.

[7] Cancer Center and Department of Medicine, University of California, San Diego.

[8] We thank Mrs. Anita Ilieff and Ms. Angela Palumbo for their help in preparation of the manuscript.

* *Reprint requests to:* Harvey Kreisman, MD, Pulmonary Division, The Sir Mortimer B. Davis-Jewish General Hospital, 3755 Cote Ste. Catherine Rd, Montreal, Quebec, H3T 1E2 Canada.

values and creatinine clearance. Doses were also reduced, if necessary, based on the Day 14 wbc and platelet counts. There was no dose escalation in either treatment arm.

All patients had measurable or evaluable disease and were TNM stage M_1 or T_3 by virtue of a malignant pleural effusion. Their CALGB performance status was 0–2. Patients who had received prior chemotherapy were ineligible; those who completed radiotherapy > 4 weeks earlier were eligible. All patients had a creatinine clearance > 60 ml/minute and adequate hemoglobin, leukocyte, and platelet counts. Required prestudy imaging included chest radiograph, liver radionuclide or ultrasound study, and bone scan. These studies were repeated as indicated. Written informed consent was obtained from all patients.

Patients were treated every 4 weeks until progression of their disease. New brain metastases were not considered to represent progressive disease and chemotherapy was continued at reduced doses (CBDCA at 300 mg/m^2 or CHIP at 180 mg/m^2) concurrent with brain irradiation in those patients. The need for radiotherapy to areas other than the CNS was regarded as evidence of progressive disease.

The patients were evaluated for response and categorized as having complete response (CR), partial response (PR; measurable disease only), tumor regression (3) (evaluable disease only), or stable/progressive disease using standard CALGB definitions. According to these definitions, a CR or PR must last > 4 weeks and tumor regression must last > 8 weeks.

Survival was measured from date of study entry to date of death from any cause or to the date of last follow-up. Survival curves were estimated using the Kaplan-Meier method (4). Differences in survival were evaluated using the log-rank test (4).

RESULTS

One hundred fifty-three patients were registered between January 1984 and January 1985. Five patients never started treatment; three were ineligible because of limited disease or significant comorbidity; and four had no follow-up data available. Thus, 70 patients treated with CBDCA and 71 patients treated with CHIP had data available for analysis. The demographic data of the two treatment groups are shown in table 1. The median age was 59 years (range, 30–83) and most patients had a performance status of 0–1 (73%) and had not received prior radiotherapy (59%). There was no difference in these prestudy characteristics between the two treatment groups.

TABLE 1.—Patient characteristics

Characteristic	Treatment	
	CBDCA	CHIP
No. of patients	70	71
Age (yrs)		
< 60	47%	52%
> 60	53%	48%
Sex		
Male	71%	69%
Female	29%	31%
Performance status		
0	33%	27%
1	36%	49%
2	31%	24%
Prior radiotherapy		
No	57%	61%
Yes	43%	39%
Cell type		
Adenocarcinoma	49%	52%
Squamous cell carcinoma	34%	30%
Large cell carcinoma	17%	18%

Of the 141 eligible patients, ten died within 60 days of beginning treatment and four others went off study before evaluation for response. They are considered as having progressive disease. The response data are recorded in table 2. Overall, 11 of 70 patients (16%; 95% confidence interval: 7%–25%) treated with CBDCA had either PR or tumor regression and five of 71 patients (7%; 95% confidence interval: 1%–13%) responded to CHIP ($P = 0.11$). Two patients with adenocarcinoma achieved CR with CHIP; no patient achieved CR after treatment with CBDCA. There was a response rate of

TABLE 2.—Response*

Cell type	Treatment	Total	Response			
			CR	PR	Tumor regression	Stable/progressive disease
Adenocarcinoma	CBDCA	34	—	2 (6)	1 (3)	31 (91)
	CHIP	37	2 (5)	1 (3)	—	34 (92)
Squamous cell carcinoma	CBDCA	24	—	4 (17)	2 (8)	18 (75)
	CHIP	21	—	1 (5)	—	19 (95)
Large cell carcinoma	CBDCA	12	—	—	2 (17)	10 (83)
	CHIP	13	—	—	1 (8)	12 (92)
Total	CBDCA	70	—	6 (9)	5 (7)	59 (84)
	CHIP	71	2 (3)	2 (3)	1 (1)	66 (93)

*Values = No. of patients (%).

TABLE 3.—Severe/life-threatening toxicity*

	Treatment	
	CBDCA	CHIP
Total	70	71
Toxicity		
Leukopenia (cells/μl)		
< 2000	5	3
< 1000	0	0
Thrombocytopenia (cells/μl)		
< 75,000	14	14
< 25,000	3	7
Hemoglobin count (g/dl)		
< 8	9	6
< 7	2	2
Nausea and vomiting		
> 2/day	8	13
Continuous	1	0
Neurotoxicity (severe)	0	1

*Values = No. of patients.

25% in 24 patients with squamous cell cancer treated with CBDCA.

The two patients with CR to CHIP are described in detail. The first patient was a 66-year-old female with primary endobronchial adenocarcinoma, brain metastases, subcutaneous nodules, and right axillary lymph node. She had a right modified radical mastectomy for suspected breast cancer but no tumor was identified pathologically. Radiotherapy was administered to the brain and thorax. Following completion of radiotherapy, she began therapy with CHIP and had complete disappearance of tumor on evaluation 1 month later. She received two more treatments but subsequently therapy was withheld because of prolonged thrombocytopenia and hepatitis B. Relapse occurred in skin nodules 3 months after achievement of CR.

The second patient, a 57-year-old male, had left upper lobe collapse, a 3.0 × 3.0-cm hilar mass, positive mediastinoscopy, and a 2.5 × 2.5-cm right adrenal metastasis on computerized tomographic (CT) scan. Prior to entry on the protocol he received radiotherapy to the thorax and warfarin sodium for a deep-vein thrombophlebitis. After three courses of CHIP the adrenal mass was no longer present on CT scan. The patient achieved CR after six courses of CHIP and relapsed in the primary site after the tenth course of chemotherapy (11 mos after beginning CHIP). He was treated with other chemotherapy but did not improve and died 11 months after documentation of progressive disease.

The maximum toxic effects on treatment are recorded in table 3. The most frequent severe or life-threatening toxic effect was thrombocytopenia (24% of patients receiving CBDCA and 30% of those receiving CHIP had platelet counts < 75,000/μl). Severe leukopenia (< 2000 cells/μl) occurred in 7% and 4% of those receiving CBDCA and CHIP, respectively. No patient had life-threatening infection and two had life-threatening hemorrhage while receiving CHIP. Nausea and vomiting of a severe degree occurred in eight patients receiving CBDCA and in 13 receiving CHIP. There was only one case of severe and continuous vomiting.

The median follow-up time for these patients is 21 months. The survival curves for all patients treated with CBDCA or CHIP are shown in figure 1. The

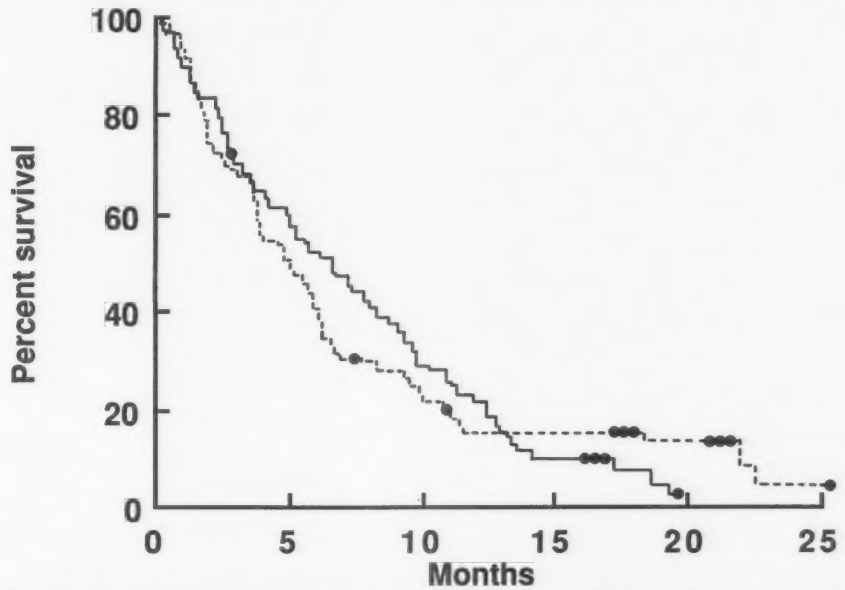

FIGURE 1.—Survival curves of all patients treated with CBDCA (——) or CHIP (----). There is no significant difference between these curves.

median survival for patients receiving CBDCA was 6.5 months; for patients receiving CHIP it was 5.0 months ($P = 0.59$).

DISCUSSION

Cisplatin is often used in combination regimens for the treatment of NSCLC. However, the use of cisplatin is limited to patients with adequate renal function and patients must be well-hydrated before and during treatment. In addition, severe nausea and vomiting is common. The cisplatin analogs used in this study may be administered without need for hydration and unlike cisplatin their dose-limiting toxic effect is myelosuppression. The nausea and vomiting experienced by patients receiving these analogs is usually mild to moderate.

We have demonstrated activity of CBDCA as a single agent in patients with advanced NSCLC. A study by Olver et al (5) showed no CRs or PRs among 41 patients treated with CBDCA. They administered CBDCA in a daily × 5 schedule every 4 weeks, whereas this study employed a single bolus every 4 weeks. The possible significance of these schedule differences is uncertain (6). In Olver's group of 41 evaluable patients, 17 (42%) had not received previous therapy; in our series, 60% had not had prior radiotherapy and none had received prior chemotherapy. Olver's study required the presence of measurable disease, whereas our patients were eligible with either measurable or evaluable disease. Five of our CBDCA responders had regression of evaluable disease (table 2) and may not have had the same degree of response (> 50% shrinkage in cross-sectional area) as that required for measurable-disease patients in both our study and Olver's trial.

The response rate in patients with squamous cell carcinoma treated with CBDCA was greater than that seen for the other histologies. However, the small number of patients in each group as well as the absence of a central pathology review make final interpretation of this observation tentative.

The intent of this study was to evaluate the two cisplatin analogs at doses near the maximally tolerated dose. Myelotoxicity was only mild to moderate in most patients and therefore higher doses of these agents would likely have been well-tolerated. We are unable to determine whether higher doses of these agents would result in increased response rates. Subsequent CALGB studies using CBDCA in combination with other myelotoxic agents will employ a dose similar to that used in this trial.

CBDCA is probably an active agent in NSCLC yet this activity did not impact on survival. Further evaluation of this drug as part of combination chemotherapy for NSCLC is warranted. Exploration of CBDCA effect in patients with squamous cell carcinomas of other organs may also be indicated.

CHIP has limited activity in patients with NSCLC. Even though there were two CRs to this therapy, further evaluation of this agent in NSCLC is unlikely to be fruitful.

REFERENCES

1. SMITH IE, and EVANS BD. Carboplatin (JM8) as a single agent and in combination in the treatment of small cell lung cancer. Cancer Treat Rev 12(suppl A):73–75, 1985.
2. WILTSHAW E. Ovarian trials at The Royal Marsden. Cancer Treat Rev 12(suppl A):67–71, 1985.
3. EAGAN RT, FLEMING TR, and SCHOONOVER V. Evaluation of response criteria in advanced lung cancer. Cancer 44:1125–1128, 1979.
4. PETO R, PIKE MC, ARMITAGE P, ET AL. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part II. Analysis and examples. Br J Cancer 35:1–39, 1977.
5. OLVER IN, DONEHOWER RC, VAN ECHO DA, ET AL. Phase II trial of carboplatin in non-small cell lung cancer. Cancer Treat Rep 70:421–422, 1986.
6. FOSTER BJ, CLAGETT-CARR K, LEYLAND-JONES B, ET AL. Results of NCI-sponsored phase I trials with carboplatin. Cancer Treat Rev 12(suppl A):43–49, 1985.

Selective Treatment of Metastatic Lymph Nodes With Combination of Local Hyperthermia and Temperature-Sensitive Liposomes Containing Bleomycin[1,2]

Soichiro Maekawa, Keizo Sugimachi,* and Masayuki Kitamura[3,4]

Temperature-sensitive liposomes are designed to break down and release their contents preferentially at temperatures attainable by local hyperthermia. The antitumor effects of hyperthermia and anticancer drugs selectively delivered by temperature-sensitive liposomes in metastatic lymph nodes in rats were determined. Temperature-sensitive liposomes containing bleomycin (BLM) were injected sc into the dorsal surface of the right hindfoot of rats bearing AH66 ascites tumor implanted 7 days previously into a right popliteal lymph node. To break down these temperature-sensitive liposomes preferentially in the metastatic lymph nodes and to achieve the synergistic effects of local hyperthermia and BLM, we applied local hyperthermia to the right popliteal lymph node by making use of a water bath at 44°C for 20 minutes. There was a significant difference in suppression of tumor growth and prolonged survival in rats receiving both temperature-sensitive liposomes containing BLM and local hyperthermia, compared with groups receiving hyperthermia alone, water solution of BLM alone, or a combination of both ($P < 0.05$). The possibility that hyperthermia plus temperature-sensitive liposomes will enhance therapy for patients with metastatic lymph nodes warrants attention. [Cancer Treat Rep 71:1053-1059, 1987]

Selective localization of antitumor drugs is a goal that, if achieved, may result in better control of the cancer. Most chemotherapeutic agents interact with nonmalignant tissue, thereby markedly reducing the therapeutic effectiveness when given systemically.

In vivo studies on the fate of liposomes injected sc showed that the liposomes are taken into lymphatics from the sc injection sites (1,2). We reported that hyperthermia alone has an antitumor effect and that synergism of hyperthermia and anticancer chemotherapy is apparent when these modalities are applied concomitantly (3,4). Based on these studies, we have now devised an even safer and more effective approach to cancer chemotherapy, using a combination of local hyperthermia and temperature-sensitive liposomes. Liposomes containing an anticancer agent were administered first, and local hyperthermia was then applied when the number of these liposomes reached a maximum in the metastatic lymph nodes.

In the present study, the antitumor effects of local hyperthermia and sc injected temperature-sensitive liposomes containing bleomycin (BLM) were determined in rat metastatic lymph nodes containing AH66 ascites tumor.

MATERIALS AND METHODS

Drugs and Chemicals

Temperature-sensitive liposomes (small unilamellar vesicle) were prepared by the method of Weinstein et al (5). The agents L-α-dipalmitoyl phosphatidylcholine (DPPC; 16 carbon chains; liquid-crystalline phase transition temperature = 41°C) and L-α-distearoyl phosphatidylcholine (DSPC; 18 carbon chains; liquid-crystalline phase transition temperature = 54°C), both from Sigma Chemical Co (St. Louis, MO), were mixed at a ratio of 70%:30% by weight. This mixture was dissolved in chloroform, dried onto the walls of a glass vial under a stream of nitrogen, and kept in a high vacuum overnight. A water solution of BLM in phosphate-buffered saline was mixed with the dried lipids, and the mixture was vortexed at 50°C. Thereafter, the mixture was sonicated at 52°C for 30 minutes with a W-375 sonicator with a cup-horn attachment (Heat Systems-Ultrasonics,

[1] Received Apr 30, 1987; revised Aug 10, 1987; accepted Aug 17, 1987.
[2] Supported in part by a grant for Cancer Research (59-5) from the Ministry of Health and Welfare and by grant 61010041 from the Ministry of Education, Japan.
[3] Department of Surgery II, Faculty of Medicine, Kyushu University, Fukuoka, Japan.
[4] We thank M. Ohara, Kyushu University, for critical comments on the manuscript.
* *Reprint requests to:* Keizo Sugimachi, MD, Department of Surgery II, Faculty of Medicine, Kyushu University, Fukuoka 812, Japan.

Inc, Plain View, NY) operating at power level 8. Liposomes were separated from the untrapped solution on a PD-10 column (Pharmacia, Uppsala, Sweden).

Animals and Tumor

Five-week-old female Donryu rats weighing 150–170 g were purchased from NIHON Rat Co, Ltd (Urawa, Japan). As a model for the metastatic lymph nodes, 4×10^6 cells of AH66 ascites tumor were inoculated into the right popliteal lymph node of the rats through a 27-gauge needle. The rats were sedated with diethyl ether. Seven days after inoculation, when the tumor was approximately 8 mm in diameter, serial studies were performed. There was no incidence of spontaneous disease regression.

Temperature Sensitivity of Liposomes

Temperature-sensitive liposomes containing 6-carboxyfluorescein (6-CF) were prepared with 2.5 mg of DPPC, 12 mg of DSPC, and 5 ml of 6-CF solution in phosphate-buffered saline (100 mmol). This suspension of the liposomes was divided into 6 aliquots and each aliquot was placed in a water bath and heated at 37°C, 38°C, 39°C, 40°C, 41°C, and 42°C, respectively. After the treatment, the fluorescence of 6-CF released from liposomes into a medium was determined, using a double-wavelength, double-beam spectrophotometer (type 557; Hitachi, Ltd, Tokyo, Japan).

Biologic Activity of Bleomycin

Seven days after inoculation of the tumor, 0.2 ml of temperature-sensitive liposomes containing BLM (210 μg/ml) and 0.2 ml of water solution of BLM (30 μg/ml) were injected into the dorsal surface of the right hindfoot. At 1, 3, 5, 7, 12, and 24 hours after this administration, the tumors in the right popliteal lymph nodes were heated to 42.5°C in a water bath at 44°C for 20 minutes, after the rats had been anesthetized with pentobarbital sodium (50 μg/kg) ip. The tissues were then excised at 1, 3, 5, 7, 12, and 24 hours after administration of the temperature-sensitive liposomes, and the same amount of saline was added. Then, the tumors were homogenized and centrifuged for 10 minutes to obtain the supernatant. To determine the biologic activity of BLM, we used the zone inhibition technique and agar plates, with *Bacillus subtilis* PCI 219 as the test organism.

Tumoricidal Effects

Temperature-sensitive liposomes containing BLM were prepared with 100 mg of DPPC, 48 mg of DSPC, and 5 ml of BLM solution in phosphate-buffered saline (3 mg/ml). The concentration of BLM contained in the liposomes was 240 μg/ml. Seven days after the inoculation, when the size of the tumor in the popliteal lymph nodes was approximately 8 mm in diameter, the rats were randomly sorted into six groups and treated as follows: Group A, no treatment as a control ($n = 13$); Group B, sc injection of liposomes containing BLM alone ($n = 13$); Group C, sc injection of water solution of BLM (BLM concentration, 500 μg/ml; $n = 11$); Group D, local hyperthermia alone ($n = 12$); Group E, sc injection of water solution of BLM followed by local hyperthermia 4 hours later ($n = 12$); and Group F, sc injection of liposomes containing BLM followed by local hyperthermia 4 hours later ($n = 12$).

In Group F, a 4-hour time interval between the injection of liposomes containing BLM and hyperthermia was maintained, based on the data of Patel et al (6) and Osborne et al (7). According to the results of our previous experiments, the activity of BLM after administration of water solution of BLM remained at a constant level for 24 hours. To establish the same conditions as for Group F, we set the 4-hour time interval between the injection of water solution of BLM and hyperthermia in Group E. The sc injection was performed at the dorsal surface of the right hindfoot, and the volumes of the injected liposomes and water solution of BLM were both 0.2 ml. Local hyperthermia was performed in a water bath at 44°C for 20 minutes, as described. The temperature of the tumor reached 42.5°C at 5 minutes after application of local hyperthermia. Tumor size of the right popliteal lymph node was estimated by measuring length (L) and thickness (T) with calipers (volume = $\frac{1}{2}LT^2$). Two weeks after this therapy, three rats each from Groups A and F were randomly selected and killed by cervical dislocation. The tumors were excised, fixed in 4% formaldehyde, embedded in paraffin, and stained with hematoxylin-eosin. Antitumor effects were compared between the tumors from the rats in Group F and those from the rats in Group A. The survival rate of the rats was monitored for each group for 50 days after the treatment. Statistical significance was determined using Student's t test.

RESULTS

Temperature Sensitivity of Liposomes

The amounts of 6-CF released from liposomes by warming at various temperatures were compared to the amount of 6-CF released from a solution of liposomes completely destroyed with Triton 100. When the liposomes were incubated at temperatures of 37°C, 38°C, 39°C, 40°C, and 41°C, little fluorescence was observed. With incubation at 42°C, the fluorescence was 82.5%, indicating an almost complete destruction of the liposomes (fig 1).

Biologic Activity of Bleomycin

Data on the biologic activity of BLM in popliteal lymph nodes containing tumor cells at various times after sc injection of liposomal BLM and water solution of BLM are shown in figure 2. One hour after the sc injection of liposomal BLM, the mean activity of BLM in the popliteal lymph nodes was 1.93 μg/g. At 24 hours after the administration, the range of the mean activity of BLM

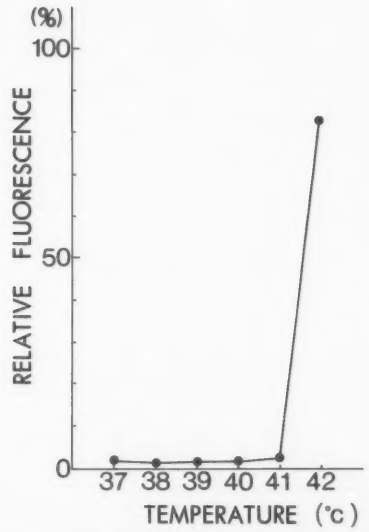

FIGURE 1.—Temperature dependence of release of 6-CF from small liposomes of DPPC:DSPC (70%:30%). Relative fluorescence with each temperature is shown as % of fluorescence against that of solution of liposomes completely destroyed with Triton 100. At 42°C, relative fluorescence dramatically increased to 82.5%.

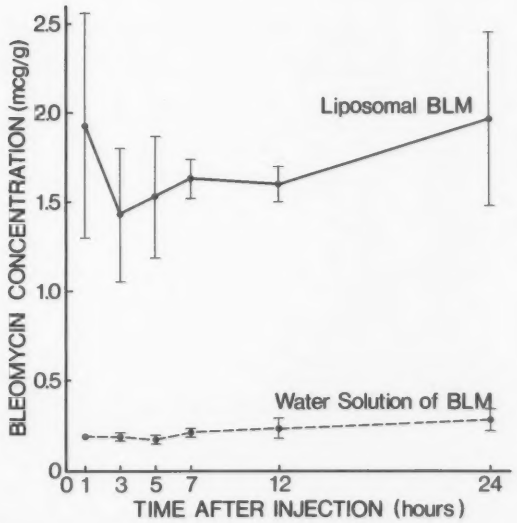

FIGURE 2.—Chronological changes of biologic activity of BLM in tumor tissue: 4×10^6 cells of AH66 ascites tumor were inoculated into right popliteal lymph node of 5-wk-old female Donryu rats. Seven days after inoculation, liposomes containing BLM and water solution of BLM were injected sc at dorsal surface of right hindfoot. Biologic activity of BLM in each popliteal lymph node at 1, 3, 5, 7, 12, and 24 hrs after injection was determined. Biologic activity of BLM in popliteal lymph nodes of rats injected with liposomes containing BLM was higher than in those given water solution of BLM. There was statistical difference between activity of liposomal BLM and that of water solution of BLM ($P < 0.01$).

was 1.43–2.36 μg/g. No peak in the activity of BLM was observed 24 hours after the injection. For 24 hours after sc injection of water solution of BLM, the activity of BLM was constant at approximately 0.2 μg/g. There was a statistical difference between the activity of liposomal BLM and that of the water solution of BLM for 24 hours after the injection ($P < 0.01$).

Tumoricidal Effects

The effects of various combinations of water solution of BLM, liposomes containing BLM, and local hyperthermia on tumor growth were determined. The ratios of tumor growth on Days 7 and 14 after treatment in each group are shown in table 1. In the control group (Group A), the size of the tumor in the popliteal lymph nodes increased gradually with time and reached 13.55 times the initial size. No tumoricidal effects were observed in groups given liposomes containing BLM without hyperthermia (Group B); water solution of BLM (Group C); hyperthermia (Group D); or water solution of BLM was hyperthermia (Group E). The volume of the tumors gradually increased to ten to 15 times the size before the therapy.

In Group F, however, the combination of liposomes containing BLM and local hyperthermia exhibited considerable tumoricidal effects. The tumor grew slowly for 1 week, reaching a growth ratio of 3.04, after which the volume ratio decreased with time to 1.20 after 2 weeks (table 1). A statistical difference was noted between Group F and all other groups ($P < 0.01$).

Histologically, almost all of the viable tumor cells were destroyed by the combined therapy of temperature-sensitive liposomes with local hyperthermia (Group F), and giant cells commonly seen in the healing stage were present in these tumors (fig 3). On the other hand, in the absence of treatment, the tumors (Group A) contained viable tumor cells with central necrosis (fig 4).

As shown in figure 5, survival rates of rats in groups A, B, C, and D decreased rapidly; rates 50 days after treatment were 7.7% in Group A; 30.8% in Group B; 9.1% in Group C; 33.3% in Group D; and 25% in Group E. Causes of death included lymph node metastases and

TABLE 1.—Effects of different treatments on tumor growth*

Group	Treatment	No. of rats	Tumor growth ratio	
			Day 7	Day 14
A	Control	13	5.91 ± 1.69	13.55 ± 4.62
B	Lip-BLM	13	6.51 ± 2.45	10.15 ± 6.13
C	W-BLM	11	6.47 ± 2.16	11.10 ± 5.59
D	HT	12	8.49 ± 3.88	15.52 ± 5.45
E	W-BLM + HT	12	9.05 ± 2.10	11.67 ± 3.46
F	Lip-BLM + HT	12	3.04 ± 0.71	1.20 ± 1.06†

*Tumor growth ratio = geometric tumor volume 7 or 14 days after treatment/geometric tumor volume at start of therapy. Lip-BLM = liposomes containing BLM; W-BLM = water solution of BLM; and HT = hyperthermia. Values = mean ± SD.

†$P < 0.01$, compared to other treatments.

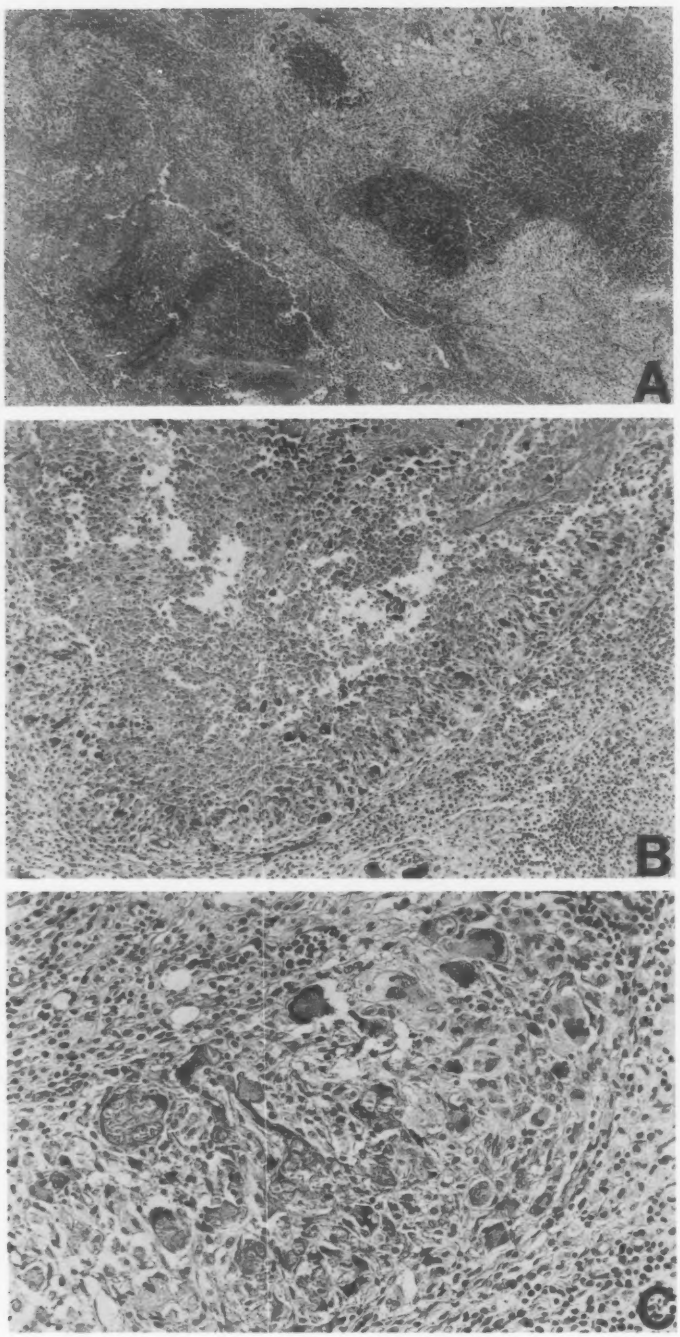

FIGURE 3.—One of right popliteal lymph nodes of Group F (treated with liposomal BLM and hyperthermia). A: Low-power view of lymph node, which was largely occupied with tumor cells. Most tumor cells were necrotic and surrounded by inflammatory and fibrous tissue (H and E; × 36). B: High-power view of same section. Necrotic tumor cells were surrounded by epithelioid cells, fibrous tissue, and inflammatory cell infiltration (H and E; × 105). C: In surroundings of necrotic tumor cells, giant cells were often seen as well as epithelioid cells and inflammatory cells (H and E; × 210).

hemorrhage around the metastases. On the other hand, no rat died for 20 days in Group F, and the survival ratio after 50 days was 75%. There was a statistical difference in the 50-day survival ratio between Group F and all other groups ($P < 0.05$); Group F versus Groups B and D ($P < 0.05$); and Group F versus Groups A, C, and E ($P < 0.01$).

DISCUSSION

Although complete dissection of regional lymph nodes will improve the survival of patients with various types of malignant tumors, such excisions are not always feasible (8,9). Therefore, we attempted to design a method of selectively targeting chemotherapy to the metastatic lymph nodes. It is conceivable that such therapy is clinically warranted to eradicate cancer cells remaining after surgical resection of the primary tumor.

In the present study, liposomes were used to selectively deliver a chemotherapeutic agent to lymph nodes containing AH66 ascites tumor cells. Although several investigators have demonstrated the possible use of liposomes as drug carriers, this concept has not been used clinically for several reasons. (*a*) The entrapment of water-soluble agents in liposomes is low. (*b*) A considerable percentage of liposomes injected iv are rapidly removed from the circulation by reticuloendothelial cells in the liver and spleen. (*c*) The membranes of liposomes are unstable, thus making long-term storage impractical (10,11). To resolve these problems, we administered a combination of local hyperthermia and sc

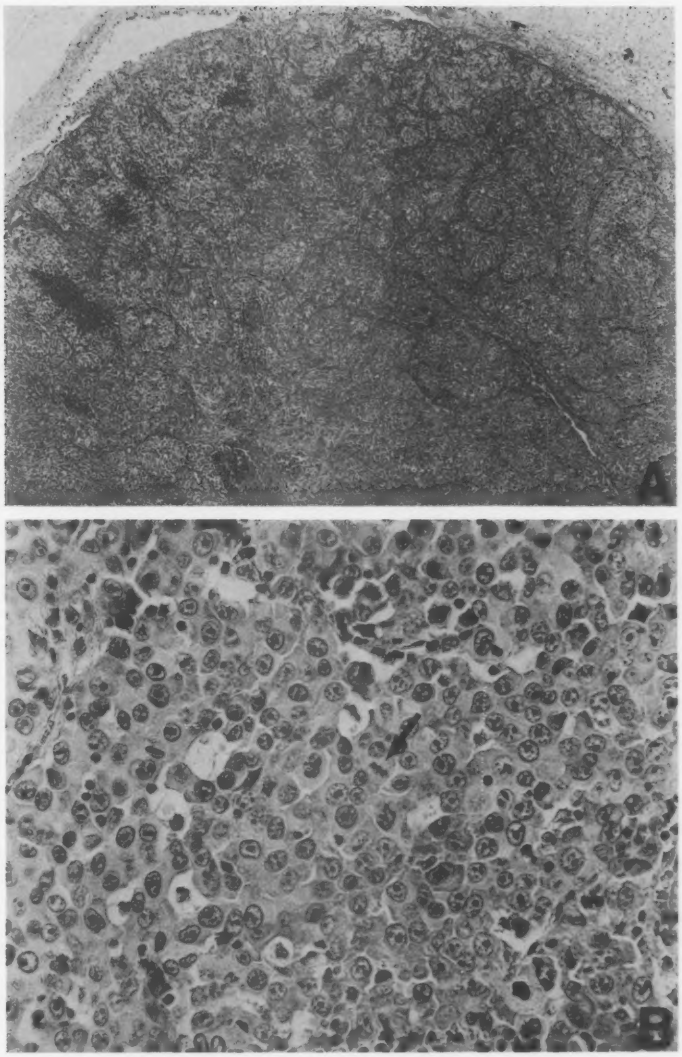

FIGURE 4.—One of right popliteal lymph nodes of Group A (without treatment). A: Low-power view of lymph node, which is largely occupied with viable tumor cells. Necrotic tissue is seldom seen (H and E; × 36). B: High-power view of tumor cells, showing basophilic cytoplasm and vacuolated nucleus with conspicuous nucleoli. Mitotic figures (arrow) are often seen (H and E; × 380).

injected temperature-sensitive liposomes as a means of targeting chemotherapy to metastatic lymph nodes. When accumulation of liposomes containing anticancer drugs reaches a maximum level after sc injection, the membrane of the temperature-sensitive liposome is destroyed considerably by local hyperthermia; thus, a synergistic anticancer effect of these two modalities can be expected (12,13). It has been reported that uptake of liposomes into regional lymph nodes was enhanced by sc administration (1,2,6,14). Weinstein et al (5), Weinstein

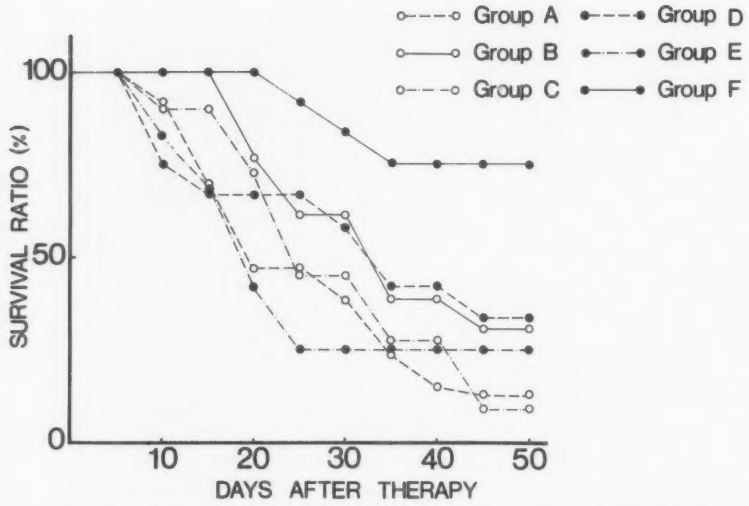

FIGURE 5.—Fifty-day survival ratios of AH66 ascites tumor-bearing rats treated with no therapy as control (Group A, $n = 13$), liposomal BLM (Group B, $n = 13$), water solution of BLM (Group C, $n = 11$), local hyperthermia alone (Group D, $n = 12$), water solution of BLM and local hyperthermia (Group E, $n = 12$), and liposomal BLM and local hyperthermia (Group F, $n = 12$). Rats were treated once 7 days after inoculation of AH66 ascites tumors. There is statistical difference between Group F and all other groups ($P < 0.05$); Group F vs Groups B and D ($P < 0.05$); and Group F vs Groups A, C, and E ($P < 0.01$).

(10), and Yatvin et al (15) found that temperature-sensitive liposomes injected iv break down and release their contents preferentially in an anatomic region subjected to local hyperthermia. We combined these two modalities and determined the therapeutic effects of liposome-hyperthermia on metastatic lymph nodes.

One of the purposes of this experiment was to investigate the specific delivery of liposomal BLM into the metastatic lymph nodes. We first used almost the same dose of liposomes containing BLM and a water solution of BLM. The activity of BLM in the popliteal lymph nodes was higher after the injection of liposomes containing BLM, compared with the water solution of BLM, presumably reflecting the rapid and preferential uptake of liposomes by regional lymphatics. This result is supported by the finding that the combined treatment with hyperthermia and liposomes containing BLM showed better tumoricidal effects, compared with the combined treatment using the double dose of water solution of BLM and hyperthermia. Other benefits of combined treatment with hyperthermia and temperature-sensitive liposomes containing BLM are the preferential release of BLM from the liposomes at a temperature $> 42°C$ and the synergistic tumoricidal effects of hyperthermia and BLM. These conclusions were supported by the finding that there were no tumoricidal effects with treatments involving water solution of BLM, hyperthermia, or hyperthermia with water solution of BLM and that only combined treatment with hyperthermia and liposomes containing BLM demonstrated suppression of tumor growth, presumably due to the synergistic effects of hyperthermia and to the high dose of BLM in the tumor. These findings suggest that a combination of hyperthermia and temperature-sensitive liposomes containing anticancer agents may have promising effects for selectively targeting metastatic lymph nodes in a clinical setting.

REFERENCES

1. KALEDIN VI, MATIENKO NA, NIKELIN VP, ET AL. Subcutaneously injected radiolabeled liposomes transport to the lymph node in mice. JNCI 69:67-70, 1982.
2. TUMER A, KIRBY C, SENIOR J, ET AL. Fate of cholesterol rich liposomes after subcutaneous injection into rats. Biochim Biophys Acta 760:119-125, 1983.
3. KITAMURA M, SUGIMACHI K, MAEKAWA S, ET AL. Destruction of VX2 tumor in rabbits by hyperthermia plus bleomycin suspended in sesame oil. Cancer Treat Rep 70:1263-1269, 1986.
4. KAI H, MATSUFUJI H, SUGIMACHI K, ET AL. Combined effects of hyperthermia, bleomycin, and x rays on Ehrlich ascites tumor. J Surg Res 41:503-509, 1986.
5. WEINSTEIN JN, MAGIN RL, CYSYK RL, ET AL. Treatment of solid L 1210 murine tumors with local hyperthermia and temperature-sensitive liposomes containing methotrexate. Cancer Res 40:1388-1395, 1980.
6. PATEL HM, BOODLE KM, and JONES RV. Assessment of the potential uses of liposomes for lymphatic drug delivery. Biochim Biophys Acta 801:76-86, 1984.
7. OSBORNE MP, RICHARDSON VJ, JEYASINGH K, ET AL. Radionuclide-labelled liposomes: a new lymph node imaging agent. Int J Nucl Med Biol 6:75-83, 1979.
8. MATSUURA H, SUGIMACHI K, HIROAKI U, ET AL. Malignant potentiality of squamous cell carcinoma of the esophagus predictable by DNA analysis. Cancer 57:1810-1814, 1986.
9. LAUNOIS B, PAUL JL, LYGIDAKIS NJ, ET AL. Results of the surgical treatment of carcinoma of the esophagus. Surg Gynecol

Obstet 156:753–760, 1983.
10. WEINSTEIN JN. Liposomes as drug carriers in cancer therapy. Cancer Treat Rep 68:127–135, 1984.
11. SEGAL AW, GREGORIADIS G, LAVENDER JP, ET AL. Tissue and hepatic subcellular distribution of liposomes containing bleomycin after intravenous administration to patients with neoplasms. Clin Sci Mol Med 51:421–425, 1976.
12. BRAUN J, and HAHN GM. Enhanced cell killing by bleomycin and 43°C hyperthermia and the inhibition of recovery from potentially lethal damage. Cancer Res 35:2921–2927, 1975.
13. SZCZEPANSKI LV, and TROTT KR. The combined effect of bleomycin and hyperthermia on the adenocarcinoma 284 of the C3H mouse. Eur J Cancer Clin Oncol 17:997–1000, 1981.
14. KHATO J, PRIESTER ER, and SIEBER SM. Enhanced lymph node uptake of melphalan following liposomal entrapment and effects on lymph node metastasis in rats. Cancer Treat Rep 66:517–527, 1982.
15. YATVIN MB, MUHLENSIEPEN H, PORSCHEN W, ET AL. Selective delivery of liposome-associated *cis*-dichlorodiammineplatinum(II) by heat and its influence on tumor drug uptake and growth. Cancer Res 41:1602–1607, 1981.

Treatment Evaluation in Active Control Studies[1]

Thomas R. Fleming[2,*]

Prospectively randomized clinical trials provide a scientifically rigorous means to evaluate the efficacy and toxicity of an experimental therapeutic intervention (EXP). Ideal designs for trials seeking to establish that EXP yields a positive effect on the primary outcome (eg, stroke rate or patient survival) involve randomization between EXP and a no-treatment control. A double-blinded randomization between EXP and placebo treatment would be preferred if the primary outcome is subjective (eg, pain relief or improvement in functional status). When an accepted standard treatment (STD) exists in a given setting, a common design is to randomize patients into the combination of STD and EXP versus STD alone, especially when it is biologically plausible to postulate synergism. With any of these designs, there is broad agreement about how standard statistical methods can be employed to assess the effect of STD on the trial's primary outcome(s).

With increasing regularity, clinical trials have been conducted using an "Active Control" design. Specifically, patients are randomized to be treated with either STD or EXP. Often this approach is motivated by an argument that randomization to no treatment would be unethical in the given setting and that the intent is to determine whether EXP could replace STD. Considerable confusion about how to design and analyze such studies has arisen when the intent simply is to establish "equivalence," rather than superiority, of the efficacy of EXP vis-à-vis that of STD. Frequently, this occurs when STD is quite toxic and the intent is to develop alternative therapies that are less toxic but equally efficacious.

In this presentation, we reconsider the primary objectives of an active control study and describe appropriate statistical methods for analysis. We focus on the special case of active control studies in the development, evaluation, and approval of oncologic drugs. The example of mitoxantrone (MITX) in advanced breast cancer is used to illustrate the relevant issues and our proposed analytical approach. In addition, we discuss the use of our approach in more general settings and provide overall recommendations.

ACTIVE CONTROL STUDIES IN EVALUATION OF ONCOLOGIC DRUGS

Since the 1962 Kefauver-Harris Amendment to the Federal Food, Drug, and Cosmetic Act, it has been required that, prior to commercial marketing of a drug, "substantial proof of efficacy" be established in addition to proof of safety. The basis for this proof of efficacy must come from "adequate and well-controlled clinical investigations" (21 CFR 314.26). A characteristic of an "adequate and well-controlled study," as stated in 21 CFR 314.26, is that "The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect." Length of patient survival and quality of life, including pain relief, are the key measures of clinical benefit (efficacy) of an investigational anticancer drug. In 1979, the U.S. Supreme Court supported this assessment by declaring that, to be effective, a cancer drug must improve either survival, quality of life, or pain. Patient survival is usually the most important of these key measures of drug efficacy. Thus, whether or not active control designs are employed, it follows from the Code of Federal Regulations that one usually needs to be able to obtain a quantitative assessment of drug effect on survival, ie, an assessment of the improvement in survival achieved by adding the drug to a regimen in which the drug has not been administered previously. We propose and illustrate a method enabling this assessment with the use of data obtained from an active control study.

Initially, we consider the setting in which the active control drug has either a negligible or only modest positive effect on survival, a very common situation for active control designs. Examples include the use of 5-fluorouracil as the active control for new drug evaluations in gastrointestinal cancer in either the advanced or surgical adjuvant setting and doxorubicin (ADR) as the active control for evaluating new regimens in advanced breast cancer.

To illustrate the issues arising in this setting, we can consider the example of the New Drug Application to the Food and Drug Administration (FDA) for market-

[1] Received Dec 31, 1986; revised July 17, 1987; accepted Aug 13, 1987.

[2] Department of Biostatistics, School of Public Health and Community Medicine, University of Washington, Seattle.

* *Reprint requests to:* Thomas R. Fleming, PhD, Department of Biostatistics SC-32, School of Public Health and Community Medicine, University of Washington, Seattle, WA 98195.

ing MITX for treatment of patients with advanced breast cancer. The drug ADR has been widely considered to be STD for such patients, undoubtedly because it has the greatest biologic activity among FDA-approved drugs. This is evidenced by its 30%–35% response rate; ie, roughly one-third of treated patients achieve transient tumor shrinkage. Unfortunately, the drug has important negative features. (*a*) It provides little or no positive benefit to length of patient survival, which usually is < 1 year for untreated patients. (*b*) It induces little or no improvement in functional status, ie, ability to walk, drive, work, or function more normally. (*c*) It provides pain relief, but this usually is only transient and is achieved in less than one-third of treated patients. (*d*) It induces considerable cardiotoxicity, alopecia, and myelosuppression.

Extensive efforts have been expended to find drugs that deliver greater clinical benefit and are less toxic than ADR. Sponsors of the new drug MITX assembled results from four studies that investigated the efficacy and toxicity of the drug (table 1). Three studies were randomized comparisons of ADR versus MITX in second-line treatment of advanced breast cancer, and the fourth study was a randomized comparison of ADR versus MITX, with each drug given in combination with 5-fluorouracil and cyclophosphamide. Thus, each of the four studies employed an active control design (transcripts of FDA Oncology Advisory Committee Meetings, Mar 14, 1986, and July 17 and 18, 1986). The sponsor found that ADR and MITX had comparable (modest to negligible) effect on ambulatory and functional status, weight gain, and pain relief. Evidence of the biologic activity of MITX was obtained, although its response rate was approximately two-thirds that of ADR in all four studies. The MITX induced significant toxicity but at reduced levels compared to ADR. With respect to patient survival, tests for consistency of the data with equality of true survival curves using two-sided log-rank statistics yielded P values > 0.05 in each study. From these analyses, the sponsor of MITX concluded that "overall survival is equivalent whether patients receive either Adriamycin or Mitoxantrone." The sponsor also concluded that commercial distribution of MITX should be permitted since it has efficacy comparable to that of the active control ADR, but at reduced toxicity; hence, MITX provides a better therapeutic index than does ADR.

Several concerns arise relating to the sponsor's analyses and conclusions. Two are focal to our discussion of the analysis of survival data from active control studies. First, nonsignificant log-rank P values (ie, $P > 0.05$) provide evidence that the data remain consistent with equality of true survival curves, but they do not establish equivalence in patient survival between the new drug and the active control; nor do they indicate how large a difference in true survival curves could exist with reasonable likelihood. [To provide a simple illustration, suppose we conduct a clinical trial in which we randomize 20 patients to each of two regimens and follow all patients until death. Even when the true survival with one regimen is double that with the other, our two-sided log-rank P value will be > 0.05 in nearly one-half of such trials (44%).] Second, even if one could establish equivalence in survival between the new drug (MITX) and the active control (ADR), it does not necessarily follow with reasonable certainty that the new drug actually has a positive effect on survival.

How then can data from active control studies be used to satisfy the stipulations of the Code of Federal Regulations requiring that we obtain a quantitative assessment of drug effect on patient survival? Fortunately, a solution does exist. It relies on two components of information: (*a*) confidence intervals that indicate how large a difference could exist with reasonable likelihood between the true survival curves of the new drug and the active control and (*b*) a reliable estimate of the active control's effect on survival. The essence of the solution is easy to state: using information on the relationship of the new drug to the active control and of the active control to no treatment, one can estimate the relationship of the new drug to no treatment and thereby obtain the desired quantitative assessment of the new drug effect.

Before developing this solution and exemplifying its use, we need a brief explanation of some important statistical terms. The "failure rate" or "hazard rate" at a given time denotes the likelihood of death over the next unit interval of time for a patient who is currently alive. When survival curves are compared, a common assumption is that the ratio of failure rates (hazard ratio) for the two curves is constant over time. For example, if the

TABLE 1.—Active control studies evaluating MITX

Study No.	Design*	No. of patients	Response rates		Survival estimate	MITX vis-à-vis ADR (95% confidence interval)†
			MITX	ADR		
3-48	CMF vs CAF	331	29%	37%	81%	58%–112%
3-40	M vs A	325	20%	29%	116%	89%–151%
3-43	M vs A	90	18%	32%	84%	49%–145%
4-52	M vs A	143	19%	30%	63%	40%–99%

*C = cyclophosphamide, F = 5-fluorouracil, M = mitoxantrone (MITX), and A = doxorubicin (ADR).

†Confidence intervals from Cox model analyses.

failure rate with STD is twice as large as that with EXP at 2 months from initiation of therapy, then it also is twice as large at 2 years or at any other point in time from initiation of therapy. This is called the proportional hazards assumption. It is a fundamental assumption when one performs Cox proportional hazards model analyses (1) or log-rank analyses (2) since such analyses provide optimal statistical power properties when the proportional hazards property does hold (3). There is an alternative interpretation for the hazard ratio. For example, if the failure rate with EXP is 1.25 times as large as that with STD (ie, EXP/STD hazard ratio = 1.25), then an approximate interpretation is that survival with STD is 25% longer than that with EXP, or equivalently, survival with EXP is 80% as long as that with STD. This interpretation is exact when survival curves are exponential. In subsequent discussion, we use this approximate interpretation and suppose that the proportional hazards assumption is reasonable.

Given these statistical concepts, we can develop a solution to obtaining a quantitative assessment of the new drug's effect on survival when data are available from active control studies. This solution can be motivated and illustrated using the active control studies evaluating MITX. For the four studies discussed earlier, table 1 provides an estimate of the relative survival on MITX with respect to ADR obtained from a Cox proportional hazards model analysis and the corresponding 95% confidence intervals. For example, in the front-line study (3-48), survival on the regimen containing MITX is estimated to be 81% as long as that on the regimen containing ADR, with a 95% confidence interval of 58%–112% for duration of survival.

Table 1 provides the first step. It allows us to quantitate the survival with MITX relative to that with ADR. A key question arises. How high must the lower bound of the 95% confidence interval be to allow the conclusion that MITX has a positive effect on survival?

Our solution to this key question will be guided by what usually constitutes evidence of a significant positive effect on survival in a "No Treatment Control" study, such as a randomized comparison of MITX versus no treatment. In such studies, evidence of a significant positive effect on survival usually is taken to be statistically significant survival improvement (Cox model or log-rank P value ≤ 0.05) of the new drug over no treatment. In turn, a P value ≤ 0.05 is equivalent to the lower bound of the confidence interval being at least 100%. Therefore, in a no-treatment control design, we obtain substantial evidence of a positive effect on survival by the new drug when the lower bound of the confidence interval of survival with the new drug versus survival with no treatment is at least 100%.

How can this standard for efficacy from a no-treatment-control design guide our development of the corresponding or analogous standard in an active control study? The answer relies on the second component of information, ie, a reasonably reliable estimate of the active control's effect on survival. Again, we can return to the MITX-ADR data to exemplify the method. A reasonable projection of the effect of the active control is that ADR provides 0%–25% improvement in survival. [*See* (4–11). There appear to be no controlled evaluations of the second-line single agent ADR providing evidence of survival improvement.] Using the more generous estimate of a 25% improvement, survival with no treatment is 80% as long as that with ADR. (The more generous the estimate, the easier it will be to establish efficacy for the new drug MITX.) It immediately follows that if survival with MITX is 80% as long as that with ADR, MITX and no treatment would be equivalent (fig 1a). Figure 1b graphically represents survival with the new drug (MITX) relative to that with the active control (ADR). By definition, ADR "resides" at 100%, while our previous estimates indicate no treatment resides at 80%. Although we do not know the point on this axis at which the efficacy of MITX truly lies, we do have the 95% confidence intervals for MITX vis-à-vis ADR. If the lower bound of this confidence interval is $> 80\%$, it is apparent from figure 1 that survival with MITX would be statistically significantly greater than that with no treatment. In turn, such a result from the active control study would be essentially equivalent to obtaining significant evidence (Cox model or log-rank P value < 0.05) from a no-treatment control study that MITX improves survival over no treatment. If the new drug is actually superior to the active control (ie, the lower bound is $> 100\%$ in fig 1b), then our criterion also is satisfied unless the active control actually decreases survival duration.

We have answered the key question regarding how high the lower bound must be. For illustration, return to the actual confidence intervals for survival with MITX relative to survival with ADR. Three of the four

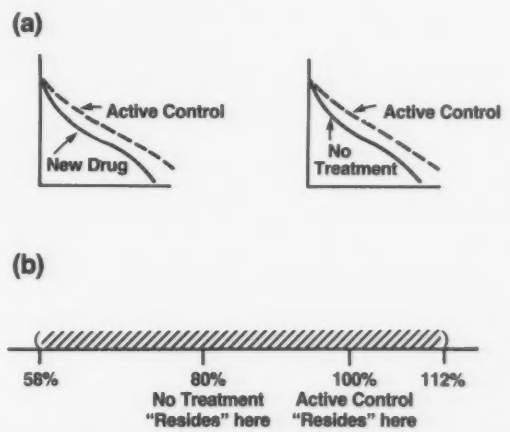

FIGURE 1.—(a) Examples of survival curves from a and b components of information, respectively. (b) Confidence interval for survival on new drug relative to active control. /// = 95% confidence interval from study 3-48.

lower bounds are considerably below 80%. In fact, data suggest that survival with MITX is roughly 80% that with ADR. If survival with no treatment is also 80% as long as that with ADR, then the data suggest that a study of MITX versus no treatment could be anticipated to have negative results. The FDA approval for marketing of MITX would then depend on evidence that it improves quality of life relative to a no-treatment approach.

We have restricted our attention to the setting in which the active control drug has either a negligible or only modest positive effect on survival. If the active control is known to provide a large survival advantage over no treatment (such as cisplatin in germ cell cancer), more stringent guidelines for new drug approval might be necessary. For example, if a relatively nontoxic active control drug is known to triple the duration of patient survival, it may no longer be adequate to establish that the new drug has a positive effect on survival; ie, it may not be adequate that the lower bound of the confidence interval for survival with the new drug versus survival with the active control is $> 33\%$. How much more stringent the standards for approval should become would depend on several factors such as the relative toxicity of the new drug and the active control.

The traditional methods of analysis of survival data from no-treatment control studies and the methods we have discussed for analysis of active control studies share a scientifically important property. These methods encourage new drug sponsors to strive to obtain high-quality data to reduce noise (eg, patients who are ineligible, inevaluable, or lost to follow-up and designs that dilute true survival differences such as crossover designs). Reducing noise results in reduction of confidence interval widths and increase in the chance of detecting positive effects of drugs. In contrast, the opposite is true when one employs the inappropriate approach of interpreting high P values (≥ 0.05) from tests of equality of survival between new drug and active control as establishing equivalence and, in turn, efficacy of the new drug. As noted by Temple (12), this latter approach encourages the use of inadequate sample sizes and noise since these lead to an increased likelihood of obtaining high P values.

DISCUSSION

We have described an appropriate statistical approach to the evaluation of clinical efficacy of new drugs when data are obtained from active control study designs. The approach relies on two key components of information: (*a*) confidence intervals for the relationship of survival with the new drug vis-à-vis survival with the active control and (*b*) a reliable estimate of the active control's effect on survival.

Both components of information are fundamentally important. Nonsignificant P values from log-rank tests (tests of equality) do not establish equality in survival between the new drug and the active control. Rather, the first component of information (confidence intervals) does provide what meaningful information can be derived from the active control study, ie, an indication of how large a difference could exist with reasonable likelihood between the true survival curves for the new drug and the active control. However, this information alone is inadequate to determine whether or not the new drug has a positive effect on patient survival. The second key component of information provides the results needed to supplement the data from the active control study. With the reliable estimate of the active control's effect on survival, one can assess the effect of the new drug on survival, as we have described.

New drug sponsors who are seeking to establish clinical efficacy of a given drug through active control studies are responsible for obtaining the best possible estimate of the therapeutic profile of the active control. The FDA has indicated (21 CFR 314.26) that in any study having an active treatment concurrent control, "The analysis should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the Active Control drug."

Suppose one seeks definitive evidence that a new drug has positive effects on the key measures of clinical benefit (efficacy), to be based on analyses described in the preceding section for active control study data. An implicit assumption in our statistical approach is that one could obtain a firm estimate (ie, one with little bias or variability) of the effect of the active control. Examples include 5-fluorouracil as an active control in adjuvant treatment of colorectal carcinoma and tamoxifen as an active control in adjuvant treatment of breast cancer in postmenopausal women with positive lymph nodes and tumors containing estrogen receptors. Recent meta-analyses have provided relatively firm estimates (13) (M. Buyse, A. Zeleniuch-Jacquotte, and T. C. Chalmers, submitted for publication) of the effects of these active controls, although issues surrounding proper interpretation of meta-analyses should be considered (14). In many applications, it is not possible to firmly estimate the active control's effect. If this second component of information cannot be readily obtained, it is imperative that the clinical effect that one presumes for the active control not be an overestimate. In a future paper, we will propose statistical methods to estimate new drug effect when one has an unreliable or highly variable estimate of the active control effect from prior studies. Methods described by Makuch and Simon (15) will be useful in that development.

No-treatment control designs obviously eliminate the need for the second component of information when one is seeking to establish substantial proof of efficacy for the new drug. In this important sense, they are superior to active control designs and should be employed whenever it is ethical and practical to do so.

Throughout our presentation, we have assumed that patient survival is the key measure of clinical benefit. One obvious motivation for this is the very short survival

expectation for most cancer patients. As noted earlier, impact on quality of life also is an important criterion by which to judge and compare investigational anticancer drugs. Attempts to quantify quality of life have included inspection of real weight gain, performance or functional status, and pain relief, with some of these being very subjective measures. Unfortunately, there has been a lack of success in identifying widely accepted measures of quality of life that can be uniformly evaluated in broad groups of patients. This has been a serious obstacle to using the effect of drugs on quality of life as a means to justify drug approval.

At times, measures that are surrogates for patient survival or quality of life are put forward. An important case is time to recurrence in adjuvant treatment of breast cancer, a disease in which patient survival usually exceeds study duration. For example, the substantial delay in time to recurrence induced by the relatively nontoxic treatment with tamoxifen means extending the period of being symptom-free and having the peace of mind that accompanies being recurrence-free. From this, we should be able to infer some improvement in quality of life and possibly in survival as well. The methods described in the previous section also would apply to evaluating drug effect on an appropriate surrogate for survival or quality of life, when using data from active control studies. However, before using any measure as a surrogate, it is important that its appropriateness be documented. For example, tumor response measures certainly are measures of biologic activity of a drug, yet they often involve soft data (16) and may provide little or no information about the impact of the drug on either survival or quality of life.

Active control study designs also are used broadly in noncancer clinical trials. For example, the effect of an experimental antihypertensive drug on lowering blood pressure may be evaluated using active control study comparisons with STD. Again, the analysis approach developed in the previous section would apply to these active control studies, even when the principal outcome is dichotomous (eg, success or failure in lowering blood pressure to the normal range) rather than continuous (eg, patient survival).

With increasing frequency in research of anticancer drugs, active control studies are conducted by seeking to develop new drugs that are less toxic than, yet equally as efficacious as, STD. Results of such trials should be interpreted cautiously. Since the objective of our therapeutic interventions is to improve survival and quality of life, despite a certain toxic cost, we should demand good evidence that the modest gains we have achieved with current STD are not lost in efforts to reduce toxicity.

REFERENCES

1. COX DR. Regression models and life tables (with discussion). J R Stat Soc B 34:187-200, 1972.
2. MANTEL N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50: 163-170, 1966.
3. GILL RD. Censoring and Stochastic Integrals. Mathematical Centre Tracts, No. 124. Amsterdam, The Mathematical Centre, 1980.
4. BULL JM, TORMEY DC, LI SH, ET AL. A randomized comparative trial of Adriamycin versus methotrexate in combination drug therapy. Cancer 41:1649-1657, 1978.
5. MUSS HB, WHITE DR, RICHARDS F, ET AL. Adriamycin vs methotrexate in five drug combination chemotherapy for advanced breast cancer—a randomized trial. Cancer 42:2141-2148, 1978.
6. AISNER J, WEINBERG V, PERLOFF M, ET AL. Chemoimmunotherapy for advanced breast cancer: a randomized comparison of 6 combinations (CMF, CAF versus CAFVP) each with or without MER immunotherapy. A CALGB study. Proc Am Assoc Cancer Res and ASCO 22:443, 1981.
7. SMALLEY RV, LEFANTE J, and BARTOLUCCI A. CAF vs CMFVP in patients with advanced breast cancer. Proc Am Assoc Cancer Res and ASCO 22:444, 1981.
8. BRINCKER H, ROSE C, VAN DE MAASE H, ET AL. A randomized study of CAF + Tam (tamoxifen) versus CMF + Tam in metastatic breast cancer. Proc ASCO 3:113, 1984.
9. TORMEY DC, WEINBERG VE, LEONE LA, ET AL. A comparison of intermittent vs continuous and of adriamycin vs methotrexate 5-drug chemotherapy for advanced breast cancer. A Cancer and Leukemia Group B study. Am J Clin Oncol 7:231-239, 1984.
10. GELBER R, and GOLDHIRSCH A. Adjuvant treatment of postmenopausal patients with breast cancer: chemo-endocrine or endocrine therapy? Proc ASCO 5:76, 1986.
11. FISHER B, WICKERHAM D, REDMOND C, ET AL. Increased benefit from addition of Adriamycin to adjuvant therapy for stage II breast cancer: results from NSABP protocols B-11 and 12. Proc ASCO 6:62, 1987.
12. TEMPLE R. Difficulties in evaluating positive control trials. Presented at the annual meeting of the American Statistical Association, Toronto, Ontario, Canada, Aug 15-18, 1983.
13. KOLATA G. Breast cancer consensus. Science 229:1378, 1985.
14. ELLENBERG S. Meta-analysis of Clinical Trials Data. ASCO Educational Booklet. Chicago, Bostrom Corp, 1987, pp 125-126.
15. MAKUCH RW, and SIMON RM. Sample size considerations for nonrandomized comparative studies. J Chronic Dis 33:175-181, 1980.
16. MOERTEL CG, and HANLEY JA. The effect of measuring error on the results of therapeutic trials in advanced cancer. Cancer 38: 388-394, 1976.

Inadequacy of Predicted Creatinine Clearance as Guide to Chemotherapy[1,2]

David F. McDermott, Armando Galindo, Raymond L. Sherman, Eric A. Jaffe, Morton Coleman, and Mark W. Pasmantier[3,*]

Many chemotherapeutic agents are nephrotoxic and/or excreted via the kidney. Thus, careful evaluation of renal function is important since drug dosages are often lowered in patients with impaired renal function. When the creatinine clearance as calculated by the method of Cockcroft and Gault from the patient's age, weight, and serum creatinine was compared to the measured creatinine clearance in the same patients, the correlation coefficient was low (r = 0.40) and the average difference between the predicted and measured creatinine clearance values was 25.3%. Thus, in our patient population, creatinine clearance calculated by the method of Cockcroft and Gault did not correlate well with measured creatinine clearance and thus was not useful as a clinical tool. [Cancer Treat Rep 71:1067-1069, 1987]

When patients are treated with chemotherapy that employs potentially nephrotoxic drugs, the initial and subsequent renal function is usually monitored by measuring creatinine and/or creatinine clearance. Unfortunately, the collection of the 24-hour urine specimens needed to calculate creatinine clearances is cumbersome. In an attempt to avoid having to collect 24-hour urine samples to estimate creatinine clearance, Cockcroft and Gault (1), using data from a study of 249 patients, developed the following formula to calculate the creatinine clearance:

$$\text{Creatinine clearance} = \frac{(140 - \text{age})\,(\text{weight in kg})}{(72)\,(\text{serum creatinine in mg/dl})}.$$

In their study, the formula was highly accurate in predicting creatinine clearance from serum creatinine in adult males; the correlation coefficient between predicted and measured creatinine clearance was 0.83. Cockcroft and Gault suggested that the predicted creatinine clearance value should be reduced by 15% when the formula was used to calculate creatinine clearance in women (1).

Our study compares the values obtained from predicting the creatinine clearance in 25 female patients with endometrial or ovarian cancer on a regimen of doxorubicin and cisplatin with the actual creatinine clearance measured in these patients using a 24-hour urine collection.

METHODS

Data were obtained from 25 female patients at The New York Hospital-Cornell Medical Center receiving doxorubicin and cisplatin for the treatment of ovarian or endometrial carcinoma.

Patients were excluded from the study if there was concurrent treatment with diuretics, antihypertensive medication, or antibiotics. The drugs doxorubicin and cisplatin were administered on an outpatient basis, with a 4-week interval between treatments. The dose of cisplatin in all of the studies was 60 mg/m^2; the dose of doxorubicin varied from 30-60 mg/m^2. The serum creatinine level and actual measured weight of the patient were noted prior to every therapy session. Creatinine clearance measurements from a 24-hour urine collection were obtained before each chemotherapy cycle. For the purpose of our study, we arbitrarily reviewed the value from before the first, second, and fifth cycles of drug administration. The mean age of our patients was 55 years, and all but one patient was Caucasian.

Serum and urine creatinine levels were determined by the Jaffe reaction as modified by Folin and Wu (2) and as further modified for performance on a Beckman ASTRA8 or a Technicon SMAC. Creatinine clearances were calculated by the method of Cockcroft and Gault (1) and reduced by 15% as suggested by them for women.

Statistical analysis was performed using an IBM PC/AT computer with 80287 math coprocessor and statistical software obtained from SYSTAT (Evanston, IL).

[1] Received Jan 12, 1987; revised Aug 10, 1987; accepted Aug 17, 1987.
[2] Supported in part by Public Health Service grants CA-07968 (National Cancer Institute) and HL-18828 (National Heart, Lung, and Blood Institute), National Institutes of Health, Department of Health and Human Services, and by funds from The Fund for Blood and Cancer Research.

[3] Divisions of Hematology/Oncology (*D. F. McDermott, A. Galindo, E. A. Jaffe, M. Coleman,* and *M. W. Pasmantier*) and Nephrology (*R. L. Sherman*), Department of Medicine, Cornell University Medical College, New York, NY.
* *Reprint requests to:* Mark W. Pasmantier, MD, 407 East 70th St, New York, NY 10021.

RESULTS

Table 1 summarizes the data obtained from the 25 patients; each patient was studied on three separate occasions. The overall (all three measurements) average predicted creatinine clearance for the group was 71.2 ± 20.3 ml/minute (mean ± SD), and the average measured creatinine clearance was 74.5 ± 21.7 ml/minute ($N = 75$; not significantly different by paired t test). While the averages for the group obtained using the two different methods were similar, the individual values obtained by the method of Cockcroft and Gault did not correlate well with those obtained by actual measurement of the creatinine clearance (fig 1). The correlation coefficient, though statistically significant, was only $r = 0.40$ ($P < 0.05$). The correlations among the three actual measurements of creatinine clearance were also calculated. Comparisons between the first and second, first and third, and second and third creatinine clearance measurements for the same patient revealed correlation coefficients of 0.42, 0.20, and 0.60, respectively. Despite this apparent low level of correlation, the values obtained by both methods were internally consistent; the coefficient of variation [CV = (100 × SD)/mean] for the three predicted creatinine clearance values was 11%, and the CV for the three measured creatinine clearance values was 18%.

When the difference between the predicted and measured creatinine clearance values was expressed as a percentage of the measured creatinine clearance, the average of the absolute differences between the paired values was 25.3%. Analysis of the individual results obtained using predicted and measured values differed by ≥ 20% in 39 (52%) of the 75 determinations and by ≥ 30% in 18 (24%). The predicted creatinine clearance was less than the measured creatinine clearance in 47 (63%) of the determinations and greater in 28 (37%).

In two patients, there was a marked difference between the measured and predicted values, which was noted on all three clearance determinations. In patient 23, the heaviest woman in our group (90 kg), the predicted creatinine clearance (100.6 ± 6.9 ml/min) exceeded the measured creatinine clearance (54.7 ± 10.3 ml/min) by an average of 89% ($N = 3$). This difference was probably due in part to a substantial increase in the predicted creatinine clearance values because of her excessive weight; in the presence of obesity, the formula for predicting creatinine clearance is less accurate (1). In patient 17, the youngest person in this study, the predicted creatinine clearance values were greater than the measured creatinine clearance by an average of 102% ($N = 3$). The average measured creatinine clearance (57.7 ± 13.4 ml/min) was low for her age (17 yrs); the reason for the large discrepancy between the predicted and measured values in this patient is unclear. A re-

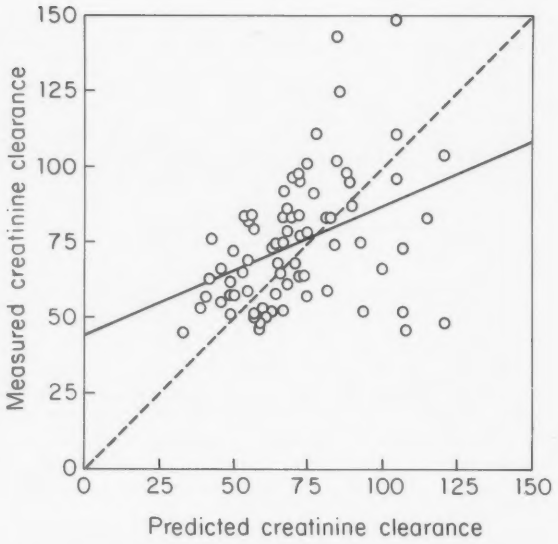

FIGURE 1.—Correlation of measured with predicted creatinine clearance. At beginning of each of 3 treatment cycles, creatinine clearances in 25 patients were measured and predicted as described in Methods. The 75 data points (measured and predicted creatinine clearance) were plotted. Dashed line represents hypothetical line of identity on which data points should fall if predicted and measured creatinine clearances are the same. Solid line represents actual regression line that was fitted to experimental data (measured = 43.819 ± 0.431 × predicted; r = 0.40).

TABLE 1.—Predicted vs measured creatinine clearance*

Patient No.	Age (yrs)	1st cycle		2nd cycle		5th cycle	
		P	M	P	M	P	M
1	53	39	53	53	65	33	45
2	57	72	84	71	68	64	58
3	62	55	69	50	72	75	101
4	58	82	83	105	149	78	111
5	58	50	57	41	57	46	55
6	51	90	87	93	75	84	74
7	60	42	63	46	66	43	76
8	62	75	78	72	98	56	84
9	64	60	53	59	48	68	61
10	47	54	83	67	83	66	65
11	38	83	83	85	102	89	95
12	53	57	50	59	46	57	79
13	49	75	57	88	98	105	111
14	47	63	73	55	69	65	68
15	61	63	52	57	51	68	86
16	57	55	82	67	75	68	78
17	19	107	52	121	48	107	73
18	32	82	59	74	64	72	95
19	49	105	96	121	104	115	83
20	63	49	62	85	143	86	125
21	61	67	92	67	52	77	91
22	49	49	57	49	51	55	59
23	29	94	52	100	66	108	46
24	40	72	64	61	50	70	97
25	60	64	74	73	77	70	83

*Values = creatinine clearance in ml/min. M = measured, P = predicted. Creatinine clearance was measured from a 24-hr urine collection before each chemotherapy cycle.

calculation of the correlation coefficient and P value excluding these patients yielded a correlation coefficient of $r = 0.66$ ($P < 0.01$).

DISCUSSION

In assessing the validity of their formula for predicting creatinine clearance, Cockcroft and Gault used creatinine clearance measurements in their normal patient population as a basis of comparison. We followed a similar approach in our patients, ie, a comparison of measured and calculated creatinine clearance. However, it is well recognized that the 24-hour urine collection is cumbersome and subject to error.

Our comparison of the measured creatinine clearance with the predicted creatinine clearance confirms that a statistically significant correlation ($r = 0.40$) exists between the two values. The correlation was improved (to $r = 0.66$) by the elimination of two cases that represented extremes in weight or age. However, even if these cases were eliminated, the correlation between the predicted and measured values ($r = 0.66$), although statistically significant, explains only 44% (r^2) of the variability between the measured and predicted values and thus is not sufficiently close to make the Cockcroft and Gault formula effective in clinical practice. Figure 1 shows many points in which there was a substantial discrepancy in creatinine clearances as estimated by the two methods. Furthermore, our comparisons of the first and second, first and third, and second and third creatinine clearance measurements revealed correlation coefficients of 0.42, 0.20, and 0.60, respectively. However, since the CV for the three measured creatinine clearance values was 18%, it is unlikely that these discrepancies are artifactual. It is more likely that these differences in measured creatinine clearance are real and are due to variations in a series of clinical factors such as changes in the state of disease (progression or improvement resulting in alteration of renal function), drug-induced renal toxicity, and overall clinical status including nutritional status and state of hydration.

The average difference between the predicted and measured creatinine clearance values was large enough so that a clinician could never be sure of the accuracy of a predicted value. Acceptance of a false low in predicted creatinine clearance would lead to underdosing, and acceptance of a false normal or high creatinine clearance would lead to overdosing, with potentially toxic chemotherapeutic agents.

In summary, the correlation between the creatinine clearance as calculated by the method of Cockcroft and Gault and the measured creatinine clearance was not high enough in these 25 women to allow use with confidence of the Cockcroft and Gault method. A study comparing inulin clearances with the two methods used in this investigation in a similar group of patients would be of value.

REFERENCES

1. COCKCROFT DW, and GAULT MH. Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41, 1976.
2. FOLIN O, and WU H. A system of blood analysis. J Biol Chem 38:81, 1919.

Management of Learned Food Aversions in Cancer Patients Receiving Chemotherapy[1,2]

Richard D. Mattes,[3,*] Cathy Arnold,[4] and Marcia Boraas[4,5]

Aversions that form towards foods after their ingestion has been associated with illness are termed learned food aversions (LFA). This adverse treatment side effect has been implicated in the anorexia of cancer and can compromise the quality of patients' lives. In an attempt to block the formation or ameliorate the manifestations of this treatment sequela, a nutritionally inconsequential "scapegoat" food was presented to patients just prior to their first course of therapy. The hypothesis was that treatment-related aversions would be targeted towards the scapegoat, thereby sparing acceptable and nutrient-dense items in the patient's typical diet. LFA were observed in 55.3% of 76 patients receiving chemotherapy for different cancers. Following formation of a scapegoat aversion, the incidence of LFA was only 11.1% (two of 18) during the 6-month follow-up period. In contrast, 48.4% (15 of 31) of the patients not exposed to the scapegoat formed LFA. More than twice as many patients with treatment-related LFA had a pretreatment histology of the problem, sugesting the presence of a subgroup of high-risk patients. Strategies for improving upon the present results are discussed. [Cancer Treat Rep 71:1071-1078, 1987]

A learned food aversion (LFA) forms when a food becomes distasteful or aversive after its ingestion has been paired with a period of illness or malaise. An estimated 38% of the general population has formed at least one such aversion (1), though the prevalence may vary markedly in different subgroups [eg, ranging from 29% among anorexia nervosa patients to 65% among one sample of college students (2)]. The nutritional impact of LFA among healthy individuals who consume a varied diet is limited since typically only a few foods are involved. Indeed, no relationship between body weight and the incidence of LFA has been identified in this population (1,2). However, LFA has been associated with weight loss among cancer patients (3) where the problem has been documented among individuals receiving chemotherapy (4,5) or radiotherapy (6). Concern regarding this treatment sequela is underscored by evidence that a patient's ability to tolerate and benefit from aggressive forms of treatment is, in part, dependent upon his/her nutritional status (7-9). The stronger association between weight loss and LFA in cancer patients may be attributable to several factors. First, since antineoplastic therapy is frequently emetogenic, there is a high probability of experiencing taste (ingestion)-illness pairings and, as a consequence, LFA. Second, cancer patients often present in a nutritionally depleted state due, in part, to self-imposed restrictions on the quantity and diversity of foods ingested. Thus, the loss of even a small number of previously acceptable foods could exert a disproportionately large influence on the adequacy of the patient's diet. It must also be recognized that the food habits of an individual reflect strongly held personal preferences and beliefs. Changes, such as those attributable to the formation of LFA, may adversely effect the quality of an individual's life, particularly that of a patient with cancer in whom the LFA may be compounding an existing problem.

Strategies for blocking the formation or ameliorating the manifestation of LFA in humans have not been systematically evaluated. One common but untested approach entails advising patients to refrain from eating for a period of time before and following a course of therapy (6,10). Fasting may help attenuate the problem (10) but, because items ingested as much as 24 hours before or after a course of therapy may be targeted for LFA [Mattes et al (11,23)], it obviously is not feasible to impose a fast of such duration surrounding each therapy session. Moreover, repeated fasts in patients undergoing multiple treatments may compound problems of weight maintenance. Nutritional counseling is a second

[1] Received Feb 18, 1987; revised Aug 13, 1987; accepted Aug 17, 1987.
[2] Supported by Public Health Service grant CA-37298 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.
[3] Monell Chemical Senses Center, Philadelphia, PA.
[4] Fox Chase Cancer Center, Philadelphia, PA.
[5] We thank Ms. Cathy Hearst, Ms. Norma Rosenbaum, and Ms. Cecilia Rooney for their assistance in data collection.
Reprint requests to: Richard Mattes, PhD, Monell Chemical Senses Center, 3500 Market St, Philadelphia, PA 19104.

strategy which is largely ineffective since the aversions result from a noncognitive type of associative learning (12). Several additional approaches have been examimed in animal studies. Numerous drugs have been administered to rats prior to aversive conditioning with chemotherapeutic agents or radiation therapy in an attempt to prevent the illness purportedly required to form an LFA (13–16). Limited success has been noted with chlorpheniramine maleate and dexamethasone, though conflicting findings have also been reported. This pharmacologic blocking approach has yet to be tested in humans. The magnitude of LFA has also been diminished in rats fed an entirely different type of diet on treatment days (17), but it is doubtful that this effect seen in rats regularly consuming a single type of diet will be applicable to humans who routinely ingest a diversity of foods in an irregular pattern. The approach currently holding greatest clinical promise stems from observations that an aversion for a particular target food can be attenuated if animals are exposed to additional taste stimuli or foods prior to the onset of illness (18–20). The intentionally introduced tastant or scapegoat food purportedly interferes with the formation of an association between the illness and dietary or target item; thus, the dietary item does not become aversive. This effect is maximized when the interfering taste stimulus is novel or unfamiliar, intensely flavored, and temporally closely paired with illness (20). Evidence suggesting this interference technique may be effective in humans has, until the present, been based upon a single study involving children prescribed GI-toxic chemotherapy. Children exposed to a novel-flavored ice cream (interference stimulus) experienced an incidence of LFA similar to that of controls, while LFA incidence was significantly higher among unexposed children (10). One additional study with adults (21) failed to confirm this finding, but in this study only a single dietary target item (cranberry juice) was monitored. The present study was designed to further investigate the hypothesis that exposing cancer patients to a novel, nutritionally inconsequential food just prior to their first course of chemotherapy could lead to a treatment-related food aversion towards the scapegoat and thereby spare nutrient-dense foods in a patient's normal diet.

METHODS

Patients

Seventy-six consecutively presenting patients meeting stipulated criteria were recruited from the in- and outpatient population of the Fox Chase Cancer Center over a 2-year period. Patients were 25–72 years of age (mean, 52 years), both male ($n = 20$) and female ($n = 56$), with a variety of histologically confirmed cancers. There was, however, a predominance of breast ($n = 34$) and lung ($n = 24$) cancers. All patients had a Karnofsky score > 60; were scheduled to receive their first course of chemotherapy; did not receive radiotherapy during the study period; were not diabetic; and were without impending bowel obstruction, physical impairments of normal ingestion, hypercalcemia, or liver or brain metastases. Head and neck cancer patients were also excluded. Thirty patients (primarily breast cancer patients) had undergone surgery and seven patients had received radiation therapy prior to recruitment.

Protocol

The study protocol is outlined in table 1. Each consenting patient was interviewed in the 60 minutes before beginning the first day of therapy. Demographic and medical information was obtained along with a record of all foods consumed for the prior 24 hours and ratings for their pleasantness and novelty. Dietary behavior was also assessed including information on pre-existing food aversions to enable newly formed LFA to be recognized. Forty-five patients (selected randomly via a random numbers table) were surreptitiously exposed to a scapegoat beverage in the hour preceding their chemotherapy. They were asked to sample and evaluate either a grape- or lemon-lime-flavored drink (flavors were counterbalanced) as part of a purported effort to develop a palatable beverage for cancer patients receiving chemotherapy. The beverages were prepared according to the manufacturer's recommendations (Kool-Aid, General

TABLE 1.—Study protocol

	15–60 mins before treatment	24 hrs after treatment	1, 2, 4, and 6 mos after treatment
Initial health and diet questionnaire	X		
24-hr food record	X	X	
Scapegoat food evaluation Form I (experimental subjects)	X		
Scapegoat food evaluation Form II (all subjects)		X	X
Follow-up health and diet questionnaire		X	X
Record of quantity of beverage(s) consumed (all subjects)		X	X

Foods Corp, White Plains, NY). Pilot tests indicated these beverages were viewed as novel (unfamiliar) if individuals were not informed of the product identity, and were sufficiently palatable to be ingested at repetitive sessions if not paired with aversive conditioning. Following completion of the first day of therapy, patients were asked to keep a record of all foods consumed for the next 24 hours. These records were mailed to the hospital upon completion (100% compliance was obtained). Subsequent interviews were conducted 1 week to 1 month, 2 months, 4 months, and 6 months later. At these meetings, subjects completed questionnaires eliciting information about their health status and dietary practices, including shifts in food preferences. In addition, they were asked to sample both fruit-flavored beverages and evaluate them on a variety of sensory dimensions irrelevant to the study purpose. They were allowed to consume as much of either beverage as they desired at each interview. Thus, the incidence of aversions was reassessed at four time points subsequent to the initiation of therapy.

Statistical Analyses

The incidence of learned food aversions was determined via three measures. First, acceptability ratings (obtained at follow-up interviews) for the items ingested in the 48 hours surrounding treatment were compared with pretreatment responses. A negative change of at least five units on a 9-point food action rating scale (22) was used as the criterion for an aversion. Second, subjects' responses to open-ended questionnaires eliciting information about foods which had become aversive or distasteful were monitored. Only items that were not identified as unpleasant or avoided prior to the initiation of treatment and had become so unpleasant that the thought of ingesting them was repugnant to the patient were considered LFA. Finally, amounts of each beverage consumed in the two-choice test were evaluated. An aversion was considered to have formed to the flavor tasted prior to the onset of therapy (scapegoat) if less than one-third of the total amount of beverage ingested (from the two fruit-flavored drinks provided) during the day's hospital visit was derived from that flavor. To determine the total number of foods which had become aversive, reports from the two measures addressing dietary items were summed, subtracting duplicate reports. The scapegoat measure only provided information regarding the formation of aversions to the fruit beverage.

To evaluate the interference effect, the incidence of aversions to foods in a patient's diet was determined for those who were and who were not exposed to the scapegoat.

Analyses were also conducted to examine the influence of selected factors (ie, age, sex, pretherapy drug use, use of antihistamines or antiemetics during therapy, pathology, stage of cancer, pretreatment weight and appetite changes, perceived changes of chemosensory function, scapegoat flavor and novelty, volume of scapegoat consumed, posttreatment illness) on the incidence of aversions to dietary foods and the scapegoat. For continuous variables (eg, weight and age) the sample was dichotomized based upon the group median value. Categorical variables (eg, sex and nausea severity) were not transformed prior to analysis. Chi-square tests using the Yates correction for continuity were used to evaluate associations. Where significant relationships were observed, lambda was calculated to assess the proportion of the variance in the dependent variable (ie, incidence of LFA towards dietary foods or the scapegoat) explained by the independent variable (eg, age and sex).

Response to chemotherapy was assessed by monitoring each patient's subjective appetite ratings, weight, and tumor response. The last measure was categorized by individuals blind with respect to the patient's LFA status as (*a*) progression of disease, (*b*) no change, (*c*) partial response, (*d*) complete disappearance of disease, or (*e*) adjuvant treatment. A loss or gain of at least 5 pounds relative to pretreatment weight was viewed as a negative or positive weight change. Patients rated their appetite as poor, moderate, or hearty and indicated whether they had noticed any change in appetite.

Because of a predominance of breast and lung cancer patients in the study population, analyses were conducted on the total population as well as on these two subgroups. An insufficient number of patients with other specific types of cancers were recruited to conduct meaningful evaluations. The breast and lung cancer subgroups held the additional advantage of facilitating an assessment of the impact of LFA on weight status and treatment outcome. Historically, breast cancer patients (stages I–III) generally maintain their weight and respond favorably to treatment. In contrast, stage II–IV lung cancer patients generally lose weight and succumb to their pathology. Thus, these two classes of patients represent the extremes of the spectrum of pertinent patient subgroups.

All patients participated in the 1-month follow-up session and 45 of 76 (59%) completed the 6-month study. Analyses of patients who were lost to study at subsequent time points failed to reveal significant differences in LFA incidence compared to active patients. Consequently, analyses involving data from the latter assessment sessions were based upon the subsample of active participants.

Statistical analyses were facilitated by the use of the Statistical Package for the Social Sciences (23). Due to the relatively small sample of patients in certain analysis groupings and the ordinal nature of some of the data, nonparametric tests were used with a probability of 0.05 set as the criterion for statistical significance.

RESULTS

Incidence and Time Course of Learned Food Aversions

Learned food aversions were observed in 42 of the 76 patients (55.3%). Following chemotherapy a total of

141 individual foods or beverages representing all food groups had become aversive, resulting in a mean of 3.3 items per affected individual. An additional 87 items were identified as less acceptable to patients, but the degree of change in attitude towards these items did not meet the criteria established for LFA. LFA occurred more than twice as often to items consumed in the 48-hour period surrounding the first course of therapy (35 patient reports) as compared to foods or beverages ingested at more distant time points (17 patient reports). During the 48-hour treatment window, 78 foods were targeted whereas 63 items consumed following this time became aversive. However, as shown in table 2, there is no clear temporal pattern of LFA onset times within the 48-hour treatment window. LFA are relatively evenly distributed throughout this time period. The only marked deviations occurred at time points when few foods were ingested, so the reliability of the data is uncertain. Diet records were collected for only the 48-hour period so the time at which ingested foods may no longer be susceptible to the formation of LFA could not be determined. The types of foods targeted for aversions are also listed in table 2 and a consideration of the onset times for items in different food groups (eg, dairy, meats, fruits, vegetables, fats, grains, and snacks) revealed no consistent pattern.

A review of the foods that had become aversive or less acceptable at more distant time points revealed a similar representation from the different food groups. A subgroup of particularly troublesome items accounted for 53% of the total. These were sweets (especially chocolate), meat products (especially red meat), caffeinated beverages (especially coffee), and high-fat or greasy foods. Additional findings on the nature of foods targeted for LFA are published elsewhere (11).

Those who formed LFA reported a higher incidence of nausea ($P = 0.042$) and emesis ($P = 0.007$) compared to those not forming LFA. A relationship was also observed between LFA formation and the severity of emetic episodes ($P = 0.006$), although this failed to reach significance for nausea severity ($P = 0.078$). The incidence or severity of such treatment-related symptoms accounted for only 18%–24% of the variance in the incidence of LFA formation. No significant association between LFA incidence and the other potentially influential treatment-related factors tested, including the use of antiemetics or antihistamines during therapy sessions, was observed. Because patients received a wide

TABLE 2.—LFA onset times, ratio of No. of aversive foods to total foods ingested in a stipulated time block, and items targeted for LFA

Time (hrs)	No. of aversive foods/ No. of foods eaten (%)	Target foods
	24-hr period preceding the first course of chemotherapy	
21–24	5/194 (2.6)	Chocolate bar, fried chicken, eggs, cookie, Cran-raspberry juice
18–21	8/190 (4.2)	Oil and vinegar dressing, olives, barbecued ribs, tamari, greens, wheat bread, hot chocolate, doughnut
15–18	6/159 (3.8)	Milk, herb tea, mayonnaise, beer, spaghetti and meat sauce, Meritene
12–15	6/38 (15.8)	Bacon, tea (2), tofu, seaweed, coffee
9–12	4/16 (25)	Rice pudding, chocolate candy, chicken broth, Italian bread
6–9	0/16 (0)	
3–6	7/121 (5.8)	Eclair, kielbasa, beef broth, toast and jelly, decaffeinated coffee (2), Jello
0–3	7/121 (5.8)	Tea, liverwurst and onions, rye bread, crackers, skim milk (2), grape-nuts cereal
	24-hr period following the first course of chemotherapy	
0–3	7/60 (11.7)	Sour cream, cottage cheese, ground beef, corn flakes, beef, water, bologna sandwich
3–6	7/129 (5.4)	Coke, tea, bean soup, brownie, water, banana, rye bread
6–9	5/103 (4.8)	Watermelon, milkshake, apple-strawberry juice, water, 7-Up
9–12	4/54 (7.4)	Water, turkey, hamburger, Hawaiian Punch
12–15	0/11 (0)	
15–18	6/48 (12.5)	Raisin Bran cereal, toast and jelly, bologna, corn flakes, All Bran cereal, gravy
18–21	5/103 (4.8)	Coffee, cheese omlet, cherry Jello, chips, whipped cream
21–24	1/138 (0.7)	Scrapple

array of chemotherapeutic agents in different combinations and doses, it was not possible to evaluate the relationship between LFA and treatment protocol. It can be noted, however, that all drugs used were associated with LFA, but no drug could be consistently implicated.

Treatment-related illness was not related to the likelihood of forming an aversion to the scapegoat. Only the volume of scapegoat consumed before treatment showed a significant positive association with the incidence of aversions for the beverage ($P = 0.004$). Volume of scapegoat consumed accounted for approximately 33% of the variance in scapegoat-directed LFA. Individuals rating the scapegoat as more novel tended to form aversions to the scapegoat more readily, but this association was not statistically significant ($P = 0.12$, lambda = 0.17).

Scapegoat Protection Effect

The incidence of LFA to foods was 40% (18 of 45) among patients exposed to the scapegoat compared to 48% (15 of 31) for those not exposed, a nonsignificant difference. The protective action of scapegoat exposure when an LFA formed for the scapegoat is demonstrated in table 3. Forty percent (18 of 45) of the patients exposed to the scapegoat beverage formed an aversion to the drink. Among these patients, the incidence of dietary LFA was only 11.1% (two of 18). All breast cancer patients remained aversion-free following their formation of an aversion for the scapegoat. Only one lung cancer patient formed an aversion for any dietary item after developing an aversion for the scapegoat. Among the other three exposed patients, one with cancer of the colon and one with prostate cancer remained aversion-free, while one patient with lymphoma did not. Patients were followed for an average of 4.5 months (range, 1–6) after the initiation of treatment and scapegoat exposure.

LFA and Outcome Measures

Patients with LFA reported a loss of appetite more frequently than those without LFA ($P = 0.016$); however, no significant association was observed between the incidence of LFA directed towards either dietary foods or the scapegoat and weight change. Tumor response did not differ significantly between patients who did and who did not form LFA.

Innate LFA Susceptibility

Approximately 32% (24 of 76) of the patients presented at the first treatment session with a history of LFA. These individuals were significantly more likely to form posttreatment LFA towards dietary foods ($P = 0.016$). Forty-five percent (24 of 53) of the patients without a history of LFA formed aversions for dietary items following the initiation of treatment, whereas 75% (18 of 24) of those with a positive history formed new LFA. Neither group demonstrated any greater tendency to form aversions towards the scapegoat. Because of the low incidence of diet-directed LFA among individuals who did target the scapegoat for an aversion, it was not possible to test whether "aversion-prone" patients fared any differently following successful targeting of the scapegoat.

DISCUSSION

Incidence and Clinical Significance of Learned Food Aversions

A previous survey of 696 individuals representing a with increasing age so that in the 46–60-year-old group LFA of 38% (1). However, there was a consistent decline with increasing age so that in the 46–60 year-old group the incidence was only about 13% and in those over 60 years of age, the incidence dropped to 6%. Since the median age of our patient population was 52 years and there were only 13 patients (17%) under the age of 46, our finding of a pretreatment incidence of 32% demonstrates a marked baseline elevation of the problem in these patients. This is consistent with animal work indicating that tumor growth alone may serve as an adequate noxious stimulus for forming food aversions (24,25). Unlike the animal literature (26), however, there was no association between the type of tumor and incidence of pretreatment LFA. Our findings are in agreement with those of another human study (3) and call into question existing animal models for LFA in cancer patients.

Once therapy began, 55.3% of the patients formed new aversions. The magnitude of the problem may be underestimated by this figure, however, since an additional 16% of the patients indicated selected foods had become

TABLE 3.—Incidence of LFA among selected cancer patients with an aversion for a scapegoat food

	No. of breast cancer patients	No. of lung cancer patients	No. of other cancer patients
No. of patients exposed (%)	16/34 (47)	17/24 (71)	12/18 (67)
No. of exposed patients with LFA towards scapegoat (%)	6/16 (38)	9/17 (53)	3/12 (25)
No. of patients with LFA towards scapegoat and food in diet (%)	0/6 (0)	1/9 (11)	1/3 (33)

less acceptable (but not actually aversive by this study's definition) following the initiation of therapy. As only 32% of the patients forming LFA reported a pretreatment history of the problem, this high incidence suggests some aspect of chemotherapy is a particularly potent stimulus for the formation of food aversions. Simply receiving chemotherapy is not an adequate stimulus for LFA development (3). Although we noted an association between the formation of LFA and treatment-related nausea and emesis, our findings and those of other studies suggest these symptoms also are not critical (5). Studies in animals have thus far failed to identify the salient feature of treatment necessary to support the formation of LFA (25,26) and less is known in humans.

Other data regarding the incidence of LFA for dietary items in patients receiving chemotherapy is limited. In one study involving children, 50% of those receiving GI-toxic chemotherapy formed LFA towards foods ingested in the 5-hour period before therapy, whereas only 12% of the children not experiencing symptoms of nausea or emesis formed aversions (17). These were newly formed aversions and are consequently indicative of a significant problem. However, children are relatively more susceptible to the formation of aversions than adults, so direct comparisons with the present findings may not be appropriate. An incidence of 56% was reported among adult chemotherapy patients, but this figure was based upon responses to a limited list of 89 foods and may therefore underestimate the problem (3). Levels comparable to those reported here have been reported in adult patients receiving radiotherapy involving the upper abdomen (6).

LFA has often been implicated in the anorexia of cancer (17,27); however, the present findings do not support this view. The frequency of changes in appetite over the 6-month follow-up period were greater among those who did form LFA relative to those who did not, although no association was noted between the incidence of LFA and weight loss. Potential changes in weight attributable to LFA may have been difficult to detect with the current study design since shifts in fluid balance and the frequent use of appetite-stimulating medications such as steroids could have masked such effects. The failure to observe a relationship between LFA and treatment outcome is not surprising since presumably any LFA-related shift in outcome would be mediated by an influence of LFA on dietary habits and nutritional status. In addition, the follow-up period may have been too limited, especially for the breast cancer patients, to observe differential effects of LFA formation on treatment outcome.

In light of advances in the management of patients with cancer, and the possibility of prolonged survival, consideration of the quality of a patient's life assumes greater importance. The adverse effects of LFA may be most pronounced in this regard. As indicated in table 2, items falling into all major food groups have become problematic. Contrary to the animal literature (28,29), highly preferred, frequently consumed foods appear to be ready targets for aversions. These foods may provide a source of pleasure and emotional stability to a patient whose life is otherwise disrupted and compromised by the sequelae of the pathology and its treatment. As a result, LFA may be expected to have a substantial negative impact on the quality of a patient's life.

Management of Treatment-Related LFA

Though it was not directly tested, the present findings indicate that certain previously recommended approaches for avoiding food aversions may be of limited value or feasibility. Antiemetic drugs and antihistamines which could reduce the severity of posttreatment complications provided no protection against LFA. Evidence that foods consumed as much as 24 hours prior to or following a course of therapy can be targeted for aversions, coupled with the absence of any gradient in susceptibility within that time period, renders the strategy of having patients fast around the time of treatment not only impractical, but of low probability of success.

The finding that aversions for foods in a patient's diet can be effectively blocked when he/she is exposed to and forms an aversion towards a nutritionally inconsequential scapegoat food prior to the initiation of therapy suggests a new approach for managing this treatment sequela. In addition to a proven effect, this treatment requires less disruption of a patient's life than fasting and, unlike the pharmacological approaches, holds essentially no risk of related undesirable side effects. Concern that the aversion to a scapegoat food may generalize to other, more nutritionally dense items in the patient's diet seems unfounded, as this was not observed in the present study and the human literature indicates that, with a few exceptions, LFA show little tendency to generalize (1,30).

Future efforts should be directed towards finding a more suitable scapegoat food than that used in the present study. Only 40% of the patients exposed to the fruit-flavored beverage used in this study formed an aversion to it and the blocking effect was significant only after the drink had become aversive. Smith et al (6) reported greater success with a similar beverage in radiotherapy patients. Nine out of ten patients refused to drink the beverage after an average of six exposures, though curiously, only 40% of the participants indicated a decreased preference for the juice. Direct comparisons between these observations and the present findings must be made cautiously, however, since the radiotherapy patients differed from those in the present study in the nature of their pathology and treatment as well as the frequency of exposure to the scapegoat. Bernstein (4) reported that only 21% of a group of children exposed to a novel ice cream before therapy selected the item again at a subsequent meeting compared to 70% of controls making that selection. In this case, however, the alternative choice was playing with a toy and not ingestion of another food. Adults exposed to the ice cream displayed no significant change in the level of ice cream

ingestion, but indicated the acceptability of the food had declined (5). Work with rats indicates certain tastes may serve as more salient stimuli for the formation of LFA (31). Similar studies have not been conducted in humans, so little is known about the attributes of a scapegoat which would make it more susceptible to the formation of aversions. Midkiff and Bernstein (32) recently reported that among a group of undergraduate students, aversions tended to be directed towards high-protein items. Similarly, meats were especially problematic to our patients. However, because of the desirability of maintaining the acceptability of this nutrient-dense class of foods, it would not be appropriate to use these foods as scapegoats. We also noted a particularly high incidence of aversions for sweet, caffeinated, and greasy items. Selected foods in each of these food groups hold little nutritional value and may be better choices, although consideration must also be given to the contribution of such items to the quality of life. In addition, though not tested here, there is animal work demonstrating solid foods, as opposed to liquids, may be particularly salient targets for food aversion learning (19). Thus, a solid food may be a more effective scapegoat. Manipulations of scapegoat taste intensity should also be evaluated in light of evidence demonstrating a positive relationship between intensity and interference effects (20).

The importance of the temporal relationship between scapegoat exposure, treatment, and food ingestion was not assessed here, but may also be important. In early animal studies, interference with food aversion learning occurred when the scapegoat was presented either before or following food intake (18). More recently, blocking was observed only when the scapegoat exposure occurred between food intake and treatment (20). The reason for these seemingly discrepant findings remains incompletely understood, as does their applicability to cancer patients. The timing of exposure to target dietary items has been controlled in the animal studies, whereas this is not possible in cancer patients who ingest and form aversions towards foods before and following treatments. The temporal relationship between scapegoat exposure and treatment in our protocol provided broad protection, but it is possible this could be enhanced if scapegoat exposure occurred at least 24 hours before treatment, when foods begin to have a higher probability of being targeted. The only patients not realizing protection following the formation of an aversion to the scapegoat had formed aversions to dietary items ingested before therapy and scapegoat exposure. Alternatively, animal studies indicate it may be preferable to present the scapegoat in close temporal proximity with the onset of treatment complications (20). Multiple exposures may also prove useful since the window of susceptibility is so wide and the onset and duration of treatment-related illness are extremely variable. However, such an approach holds the risk of rendering the scapegoat more familiar to patients and therefore less likely to be targeted and effective (20).

Scapegoat-directed aversions might also be maximized by selecting a novel-tasting food and encouraging patients to ingest as much of the item as possible. A significant association was noted between the volume of scapegoat ingested before therapy and the subsequent incidence of aversions to the beverage. Novelty ratings also tended to be positively associated with aversions to the scapegoat. This is consistent with an extensive animal literature including nonhuman primates (33) as well as survey results with humans (30).

Finally, it should be noted that the observation of higher rates of LFA among patients who present with a prior history of such a problem is consistent with recent selective breeding work with rats (34). These studies demonstrate a genetic basis for susceptibility to food aversion learning. No attempt was made to ascertain the aversion experience of patients' family members in this study. If humans are found to exhibit a genetic or familial proclivity for LFA, knowledge of the patient's aversion history coupled with that of appropriate family members may allow reliable identification of at-risk patients and therefore efficient administration of intervention strategies.

In summary, the present study demonstrates cancer patients receiving chemotherapy experience a high rate of LFA. Although these aversions were not found to impact on a patient's weight or treatment outcome in this relatively short-term study, they clearly hold the potential to negatively influence the quality of a patient's life. Exposure to a nutritionally inconsequential scapegoat food just prior to the onset of the first course of chemotherapy was found to interfere with the formation of aversions for items in the patient's typical diet when an aversion was formed towards the scapegoat item. Thus, nutrient-dense and highly preferred foods remain acceptable. Further refinement of means to identify patients at high risk of forming LFA and identification of scapegoat foods more reliably targeted for LFA should make this simple, essentially risk-free intervention strategy useful in the management of chemotherapy patients.

REFERENCES

1. GARB JL, and STUNKARD AJ. Taste aversions in man. Am J Psychiatry 131:1204-1207, 1974.
2. LOGUE AW, LOGUE KR, and STRAUSS KE. The acquisition of taste aversions in humans with eating and drinking disorders. Behav Res Ther 21:275-289, 1983.
3. NIELSEN SS, THEOLOGIDES A, and VICKERS ZM. Influence of food odors on food aversions and preferences in patients with cancer. Am J Clin Nutr 33:2253-2261, 1980.
4. BERNSTEIN IL. Learned taste aversions in children receiving chemotherapy. Science 200:1302-1303, 1978.
5. BERNSTEIN IL, and WEBSTER MM. Learned taste aversions in humans. Physiol Behav 25:363-366, 1980.
6. SMITH JC, BLUMSACK JT, BILEK FS, ET AL. Radiation-induced taste aversion as a factor in cancer therapy. Cancer Treat Rep 68:1219-1227, 1984.
7. COPELAND EM, DALY JM, and DUDRICK SJ. Nutrition as an adjunct to cancer treatment in the adult. Cancer Res 37:2451-2456, 1977.

8. TOMINAGA T, ONODERA T, KITAMURA M, ET AL. Combined treatment by chemotherapy and intravenous hyperalimentation in Japanese patients with advanced breast cancer. Cancer 46:642–646, 1980.
9. RICKARD KA, DETAMORE CM, COATES TD, ET AL. Effect of nutrition staging on treatment delays and outcome in stage IV neuroblastoma. Cancer 52:587–598, 1983.
10. BERNSTEIN IL, WEBSTER MM, and BERNSTEIN ID. Food aversions in children receiving chemotherapy for cancer. Cancer 50: 2961–2963, 1982.
11. MATTES RD, ARNOLD C, and BORAAS M. Learned food aversions among cancer chemotherapy patients: incidence, nature and clinical implications. Cancer, in press.
12. SELIGMAN MEP, and HAGER JL. Biological Boundaries of Learning. New York, Appelton-Century-Crofts, 1972.
13. LEVY CJ, CARROLL ME, SMITH JC, ET AL. Antihistamines block radiation-induced taste aversions. Science 186:1044–1046, 1974.
14. SESSIONS GR. Histamine and radiation-induced taste aversion conditioning. Science 190:402–403, 1975.
15. CAIRNIE AB, and LEACH KE. Dexamethasone: a potent blocker for radiation-induced taste aversion in rats. Pharmacol Biochem Behav 17:305–311, 1982.
16. RABIN BM, and HUNT WA. Effects of antiemetics on the acquisition and recall of radiation- and lithium chloride-induced conditioned taste aversions. Pharmacol Biochem Behav 18:629–635, 1983.
17. BERNSTEIN IL, and BERNSTEIN ID. Learned food aversions and cancer anorexia. Cancer Treat Rep 65(suppl 5):43–47, 1981.
18. REVUSKY SH. The role of interference in association over a delay. *In* Animal Memory (Honig WK, and James H, eds). New York, Academic Press, 1971.
19. FENNER DP, and BERNSTEIN IL. Interference in food aversion conditioning by reducing drug dose or conditioning trials. Behav Neural Biol 40:114–118, 1984.
20. CANNON DS, BEST MR, BATSON JD, ET AL. Interfering with taste aversion learning in rats: the role of associative interference. Appetite 6:1–19, 1985.
21. CANNON DS, BEST MR, BATSON JD, ET AL. Taste familiarity and apomorphine-induced taste aversions in humans. Behav Res Ther 21:669–673, 1983.
22. SCHUTZ HG. A food action rating scale for measuring food acceptance. J Food Sci 30:365–374, 1965.
23. SPSS, Inc. SPSS/PC+ for the IBM PC/XT/AT. SPSS, Inc.: Chicago, 1986.
24. BERNSTEIN IL, and SIGMUNDI RA. Tumor anorexia: a learned food aversion? Science 209:416–418, 1980.
25. BERNSTEIN IL, TRENEER CM, GOEHLER LE, ET AL. Tumor growth in rats: conditioned suppression of food intake and preference. Behav Neurosci 99:818–830, 1985.
26. BERNSTEIN IL, and FENNER DP. Learned food aversions: heterogeneity of animal models of tumor-induced anorexia. Appetite 4:79–86, 1983.
27. SCHEIN PS, MACDONALD JS, WATERS C, ET AL. Nutritional complications of cancer and its treatment. Semin Oncol 2:337–347, 1975.
28. REVUSKY SH, and BEDARF EW. Association of illness with ingestion of novel foods. Science 155:219–220, 1967.
29. ELKINS RL. Attenuation of drug-induced bait-shyness to a palatable solution as an increasing function of its availability prior to conditioning. Behav Biol 9:221–226, 1973.
30. LOGUE AW. Conditioned food aversion learning in humans. *In* Experimental Assessments and Clinical Applications of Conditioned Food Aversions (Braveman NS, and Bronstein P, eds). Ann NY Acad Sci 443:316–329, 1985.
31. KALAT JW, and ROZIN P. "Salience": a factor which can override temporal contiguity in taste-aversion learning. J Comp Physiol 71:192–197, 1970.
32. MIDKIFF EE, and BERNSTEIN IL. Targets of learned food aversions in humans. Physiol Behav 34:839–841, 1985.
33. MATSUZAWA T, and HASEGAWA Y. Food aversion learning in Japanese monkeys (*Macaca fuscata*). Folia Primatol (Basel) 40: 247–255, 1983.
34. ELKINS RL. Separation of taste-aversion-prone and taste-aversion-resistant rats through selective breeding: implications for individual differences in conditionability and aversion-therapy alcoholism treatment. Behav Neurosci 100:121–124, 1986.

How Large Should a Phase II Trial of a New Drug Be?[1]

Richard Simon[2,*]

A number of statistical designs for phase II trials have been published. These designs are critically reviewed. A new design is also introduced. Data are presented on the response rates observed for new chemotherapeutic agents introduced by the National Cancer Institute since 1975. Based upon this material, it is recommended that two-stage designs with a target sample size of 35–50 patients and substantial probability of early termination are usually appropriate. It is also recommended that for active drugs, two to three such trials are necessary to estimate the response rate with reasonable precision. Precise estimation of phase II response rates is not always important, however. For very rare diseases or situations where several dose levels of a biologic are to be evaluated, selection designs may be most appropriate. Such designs are described. Tables are presented to facilitate the design of new agent phase II clinical trials. [Cancer Treat Rep 71:1079–1085, 1987]

New drugs are needed for the treatment of most human malignancies. Phase II studies are important because the antitumor activity of a new agent is first determined by such trials. Important aspects of the design of phase II studies have recently been critically assessed (1,2), but here we shall focus on the issue of the size of phase II studies of new agents. Several statistical approaches to establishing the size of a phase II study have been published. These approaches do not provide specific sample sizes until one specifies parameters such as desired error limits, standard errors, or target activity levels. In this manuscript we shall critically review these statistical approaches and introduce a new approach. We shall also present data concerning the activity levels of previously studied new agents and make recommendations concerning appropriate numbers of patients for phase II studies of single agents.

GEHAN'S PHASE II DESIGN

The oldest and most commonly used design was introduced by Gehan (3). It is a two-stage design for estimating the response rate but providing for early termination if the drug shows insufficient antitumor activity. The design is most commonly used with a first stage of 14 evaluable patients. If no responses are observed then the trial is terminated. The rationale for stopping is that if the true response probability were at least 20%, then at least one response would very likely have been observed in the first 14 patients. Since no responses were seen, it is unlikely that the true response probability is at least 20%. If the target level of activity of minimum interest is different than 20%, then a first-stage sample size other than 14 would be appropriate.

If at least one response is observed in the first 14 patients, then a second stage of accrual is carried out to obtain an estimate of the response rate. The number of patients to accrue in the second stage depends upon the number of responses observed in the first stage and upon the precision desired for the final estimate of response rate. If the first stage consists of 14 patients, then the second stage will consist of between one and 11 patients if a standard error of 10% is desired. The second stage will consist of between 45 and 86 patients if a standard error of 5% is desired.

Gehan's design has been very popular, and sometimes has been misused. Some investigators seem to think that all phase II trials should have exactly 14 patients; they forget that a second stage of accrual is required if any responses are observed in the first stage. The design with a first stage of 14 patients and a second stage of 11 patients, for a total of 25 patients, is the variant that has been most commonly used. This provides an estimator of response rate with a standard error of about 10%. There is, however, no obvious reason for believing a standard error of 10% is appropriate. A standard error of 10% corresponds to very broad confidence limits. For example, if three responses are observed among 25 patients, a 95% confidence limit for the true response rate is from about 3% to about 30%. Requiring that the

[1] Received Feb 17, 1987; revised June 22, 1987; accepted July 16, 1987.
[2] Biometric Research Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD.

*Reprint requests to: Richard Simon, PhD, Biometric Research Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Landow Bldg, Rm 4B06, National Institutes of Health, Bethesda, MD 20892.

standard error be 5% instead of 10% provides estimates with more satisfactory precision, but requires much larger sample sizes. If the second stage is to be much larger, however, then it is not clear that the first stage should be limited to 14 patients. This is because even for a poor drug with a true response rate of 5%, there is a 51% chance of obtaining at least one response among the first 14 patients. Consequently, the first stage of 14 patients would not effectively screen out inactive drugs.

FLEMING'S DESIGN

Fleming (4) presented a multistage design for testing a null hypothesis H_0: $p \leq p_0$ that the true response probability is less than some uninteresting level against an alternative hypothesis H_1: $p \geq p_1$ that the true response probability is at least as large as a target level p_1. We will refer to a drug with response probability $\geq p_0$ as "active" and a drug with response probability $\geq p_1$ as "highly active." If one specifies the number of stages desired, the target levels p_0 and p_1 and the error limits α for accepting an inactive drug and β for rejecting a highly active drug, then designs of this class can be determined. Consider a design with $p_0 = 0.05$ and $p_1 = 0.20$ for which both error limits are to be < 0.10. These constraints can be met with a two-stage Fleming design having 15 patients in the first stage and 20 in the second stage. If no responses are observed among the first 15 patients, then the trial is terminated and the drug is rejected. If at least three responses are observed among the first 15 patients, then the trial is terminated and the drug is accepted. If one to two responses are observed among the first 15 patients, then 20 more patients are accrued. After all 35 patients are evaluated, the drug is accepted if the response rate is $\geq 11.4\%$ (four responses among 35 patients) and the drug is rejected if the response rate is $\leq 8.6\%$ (three responses among 35 patients). Table 1 shows some other Fleming designs.

Fleming's design is attractive because it forces one to specify levels of activity of interest and to attempt to define how decisions will be influenced by results. One must bear in mind, however, that acceptance of the drug for later study does not imply that it is highly active. For example, the drug is accepted if the observed response rate is 11.4% (four responses among 35 patients). With $p_0 = 0.05$, acceptance of the drug merely indicates that the drug is active, ie, produces responses above a background rate of 5%. Rejection of the drug means that there is strong evidence that the drug is not highly active. It does not mean that the drug is inactive. For example, the drug is rejected when the observed response rate is 8.6% (three responses among 35 patients). The design provides a sample size large enough to ensure that if the drug is either inactive or highly active then the appropriate decision will be reached by the end of the trial with the specified error probabilities. For $p_0 = 0.05$, $p_1 = 0.20$, and error probabilities $< 10\%$, a maximum sample size of 35 patients is adequate. If the drug is accepted, the design does not itself specify how much further study of the drug is appropriate. For interpreting results after use of Fleming's design it is useful to employ confidence intervals (5–7). Such intervals make clear what is consistent with the results and what is not and avoids the potential misinterpretations that may result from accept-reject terminology.

OPTIMAL TWO-STAGE EARLY REJECTION DESIGNS

Two aspects of Fleming designs can limit their applicability. First, it is often not desirable to terminate a phase II trial early when the drug is determined to be active; ie, has a response probability $> p_0$. In that circumstance it may be appropriate to study additional patients to estimate the rate, extent, and durability of response, because p_0 may represent a background noise level. Second, it is based on an approach developed for phase III trials (8) in which early rejection of a hypothesis occurs only when interim results are very extreme. This conservatism permits final analysis to be unaffected by interim monitoring if early termination does not occur. This is very desirable for phase III trials but seems less appropriate for phase II trials of new agents. Traditionally, such drugs are mostly inactive.

An alternative approach is to specify the design parameters p_0, p_1, α, and β and then determine the two-stage design that satisfies the error probability constraints and minimizes the expected sample size when the true response probability is a specified value p. The value p should represent the response probability that is a priori most likely. The optimization is taken over all

TABLE 1.—Fleming designs

				Reject drug if response rate—		Accept drug if response rate—					
p_0	p_1	n_1	n	$\leq r_1/n_1$	$\leq r/n$	$\geq a_1/n_1$	$\geq a/n$	α	β	PET*	ANP†
0.05	0.25	15	25	1/15	2/25	3/15	3/25	0.09	0.09	0.83	16.35
0.05	0.20	15	35	0/15	3/35	3/15	4/35	0.10	0.08	0.46	25.00
0.10	0.25	20	40	1/20	6/40	5/20	7/40	0.11	0.10	0.74	25.20

*PET = probability of early termination rejecting the drug after n_1 patients if the true probability of response is 0.05.

†ANP = average No. of patients entered before a decision if the true probability of response is 0.05.

TABLE 2.—Optimum designs for $\alpha = \beta = 0.10$, $p = 0.05$

p_0	p_1	n_1	n	Reject drug if response rate— $\leq r_1/n_1$	$\leq r/n$	PET*	ANP*
0.05	0.25	9	24	0/9	2/24	0.63	14.55
0.05	0.20	12	37	0/12	3/37	0.54	23.50
0.10	0.25	16	49	1/16	7/49	0.81	22.27
0.20	0.40	17	37	3/17	10/37	0.55†	26.00

*See table 1 legend.

†This design is optimized for a true response rate of 0.20. PET and ANP are calculated at that point.

values of n_1 and n. Early acceptance of the drug (rejection of H_0) is not permitted.

Table 2 shows some such optimal designs. In all cases we have used $\alpha = 0.10$, $\beta = 0.10$, and $p = 0.05$. As will be seen later, the value $p = 0.05$ is based on past experience that most drugs have been inactive for most solid tumors. Using $p = 0.05$ is not inconsistent with having $p_0 = 0.10$. It merely indicates that although we want the probability of accepting a 10% drug limited to α, we want the design optimized to minimize the expected sample size for a 5% drug.

The right side of table 2 shows the optimal size of the first stage (n_1), the maximum sample size (n), and the upper limits on observed response rates that result in rejection of the drug at the end of the first stage (r_1/n_1) and at the end of the trial (r/n). The column labeled PET gives the probability of terminating the trial at the end of the first stage if the true response probability is 0.05. The last column gives the average sample size when the true response probability is 0.05. It is the average sample size that has been optimized. For example, the second line in table 2 corresponds to a design with $p_0 = 0.05$ and $p = 0.20$. The first stage consists of 12 patients. If no responses are seen then the trial is terminated. Otherwise, accrual continues to a total of 37 patients. The probability of early termination is 0.54 for a drug with a true response probability of 0.05. The average sample size is 54% times 12 plus 46% times 37, or 23.50. This design is fairly similar to the Fleming design described in the previous section if we ignore the possibility of early acceptance of the drug. In that design we had arbitrarily specified the initial stage to consist of 15 patients and the maximum sample size to be 35 patients. In many cases, the optimal designs are not "modified Fleming designs" (ie, Fleming designs in which we ignore the possibility of early acceptance of the drug). The average sample sizes for the designs shown in table 2 are less than those for the corresponding designs in table 1. The comparison is not entirely appropriate, however, because the error probabilities are not identical and because Fleming designs can accept the drug after the first stage.

The optimal two-stage designs achieve optimality by a combination of keeping the size of the first stage fairly small, making the continuation criteria stringent so that the probability of rejecting an inactive drug after the first stage is high, and not permitting too large a second stage. The optimal two-stage designs do not necessarily minimize the maximum sample size n subject to the error probability constraints. For example, the third design in table 2 has a maximum sample size of 49 patients. There is a two-stage design based on a maximum of 40 patients that also satisfies the error constraints. That design has $n_1 = 23$, $r_1 = 1$, $r = 6$. The expected sample size for that design, however, is 28.45, a 28% increase over the expected size of 22.27 for the optimal design.

The last design listed in table 2 was optimized for $p = 0.20$ instead of 0.05. It may be appropriate for phase II studies of new drugs in leukemia or lymphoma.

SYLVESTER-STAQUET DESIGNS

Sylvester and Staquet (9) have attempted to determine optimal sample sizes by quantifying the ethical costs to the patients of treatment with active or inactive phase II drugs. They assume that the ethical cost of treating a patient with a drug having a response rate p is proportional to $p_s - p$, where p_s may be thought of as the response rate achievable with some standard therapy. They assume that following the phase II trial the drug will either be dropped from further study or accepted and administered to m patients as a single agent in a phase III study. They also assume that there is an expected horizon of t patients who could be treated with this drug if it has a response rate greater than p_s before another such effective drug comes along.

Sylvester and Staquet (9) also assume that the true response probability either has a lower value p_0 that is not of much interest or that it has a larger value p_1. The response probability p_s is taken to be between p_0 and p_1. One is also required to specify the a priori likelihood π that p equals p_0 rather than p_1. If one imposes the requirement that the probability of rejecting a drug with activity level p_1 must be a small-value β, then the expected loss function simplifies and becomes independent of the horizon t.

Hence, if one specifies m, p_0, p_1, β, and p_s, a value of the phase II sample size n that minimizes ethical costs can be determined. Table 3 indicates that for $p_0 = 0.05$,

TABLE 3.—Sylvester-Staquet designs*

A priori probability that p = 0.05	No. of patients/treatment in phase III trial	Optimal single-stage phase II sample size
0.90	75	29
0.90	100	36
0.90	125	37
0.50	75	43
0.50	100	43
0.50	125	43

*Assumed values: $p_0 = 0.05$, $p_1 = 0.20$, $p_s = 0.15$, and $\beta = 0.05$.

$p_1 = 0.20$, $p_s = 0.15$, $\beta = 0.05$, and m in the range 75–125, a sample size in the range of 30–40 is considered optimal by this approach. This table is based on using a single-stage, phase II trial, but results for two-stage trials do not differ substantially.

The Sylvester-Staquet approach is very interesting and goes further than most other approaches in trying to specify the decision-making objectives of phase II trials. It is arguable, however, whether the "cost" function employed is entirely appropriate. For some solid tumors, partial responses may not extend survival or improve quality of life. Hence, it may not be appropriate to base the ethical cost of treatment upon the degree to which the response rate of the new drug differs from the response rate of the standard. Another difficulty is the assumption that a drug not rejected in a phase II trial will then be compared as a single agent to the standard treatment in a phase III trial. Although this may sometimes be the case, it is also possible that the drug will be included in a combination regimen. In such a case the loss function used by Sylvester and Staquet (9) would not be appropriate. There may be no standard or effective treatment for patients of the type considered. Finally, the assumption that the true response probability is either a low-level p_0 or a satisfactory-level p_1 may not always be appropriate.

OTHER DESIGNS

Several other statistical designs should be mentioned. Lee et al (10) present two-stage designs for testing a hypothesis $p \geq p_1$ (say 0.20) against the alternative hypothesis $p < p_1$ in which three final decisions are possible. One may reject the hypothesis $p \geq p_1$ and the drug, one may reject the hypothesis $p < p_1$ and conclude that the drug has a response probability of at least p_1, or one may conclude that the data are insufficient to decide whether the true response probability is $>$ or $< p_1$. Although this formulation is reasonable, the designs published had large probabilities of accepting a poor drug and large probabilities of obtaining an inconclusive result.

Herson (11) introduced predictive probability early-termination plans. A single-stage trial is designed for testing a hypothesis $p \geq p_1$ against the alternative $p < p_1$. The decision rule is based on whether the number of responses at the end of the trial is $\leq L$ or $> L$. Herson suggests that at various points during the trial one calculates the "predictive probability" that at the end there will be $> L$ responses given the data at that point and prior expectations. If the predictive probability is either very large or very small, then the outcome is almost certain and the trial can be terminated early. The actual probability of $> L$ responses at the end depends on the unknown true response probability. The predictive probability is calculated with regard to the prior distribution of response probabilities as well as the interim results. The prior distribution specifies what the likelihoods of low, intermediate, and high response probabilities are considered to be at the start of the trial before data are available. Although predictive probabilities may be attractive in some ways, it is not clear that the fact that most drugs are negative should influence the adequacy with which we test a specific new drug. Such an approach reduces the number of patients exposed to inactive drugs at the cost of increasing the probability of missing a good drug.

DESIGNS FOR SELECTING AMONG DRUGS

In some cases the objective of a phase II study involves selecting a promising agent from among a set of candidates in addition to or instead of evaluating each of the candidates. For example, we may wish to select the best dose level for a phase III trial of a biologic based upon a randomized phase II trial of two or more dose levels. Or we may wish to select for phase III trial a preparation of a drug from among many possible preparations.

Although these objectives are comparative, the usual statistical sample size formulas for phase III trials are not always appropriate. For example, if we are interested only in selecting a promising dose rather than in really testing the hypothesis that there is no dose-response effect, then a selection formulation rather than a hypothesis-testing formulation is appropriate. This distinction is important from a sample size standpoint, and one should carefully consider the objectives of a phase II study involving comparison or selection. Some randomized phase II studies are actually inadequate phase III trials.

Simon et al (2) studied randomized phase II trials for selecting the best from among a small set of candidate treatments. The selection formulation assumes that the treatment which produces the greatest response rate will be selected for a subsequent study regardless of how small that apparent superiority is. The sample size is based on the constraint that if one treatment is in fact superior by an amount D, then the probability of correctly selecting it must be at least P. Table 4 shows the required number of patients per treatment if D = 15% and P = 0.90. The sample size depends somewhat on the number of candidate treatments and the baseline response probabilities but are mostly in the range of 20–60 patients per treatment.

Whitehead (12) introduced a model for selecting among a large number of treatments. He assumed that

TABLE 4.—No. of patients per treatment for selection design*

Smallest response rate (%)	No. of treatments		
	2	3	4
10	21	31	37
20	29	44	52
30	35	52	62
40	37	55	67
50	36	54	65
60	32	49	59
70	26	39	47
80	16	24	29

*Probability of correctly selecting best treatment is 0.90 when it is superior by absolute difference of 15% in response rate. Values = No. of patients.

there is some distribution of true response probabilities and that the true response probability of a specific treatment is drawn from that distribution. With a limited number of patients and a large number of treatments there is a trade-off between the adequacy with which each treatment can be evaluated and the number of treatments that can be studied. By reducing the adequacy of evaluation of individual treatments one can test more treatments and they may have higher response probabilities. The objective is the selection of a single promising treatment rather than the evaluation of the treatments. Whitehead studied this approach assuming a beta distribution for the true response probabilities. He concluded that such phase II trials should have very few patients per treatment but that was based on distributions that provided substantial likelihood that very active treatments were lurking among the candidates. If there are such treatments then they will be recognized in small trials as long as they are tried.

RESPONSE RATES FOR PHASE II AGENTS

The appropriate size of a phase II trial depends upon the levels of activity that one is attempting to distinguish. Consequently, it may be of some value to review the response rates that have been found in single-agent phase II studies. Table 5 summarizes response rates found for 83 cytotoxic drugs entering clinical trial under National Cancer Institute sponsorship from 1970 to 1985 (13). An overall response rate for each drug in each tumor type was calculated by pooling all results. The table includes entries for which the number of patients was at least 25 and entries for which there were 14–24 patients with no responses.

The data include trials of good and poor quality and span a period of time in which the characteristics of patients entered on phase II trials changed considerably. There are many other caveats one can cite. For these data, however, response rates for solid tumors cluster in the < 5% interval and most drugs were very inactive in the kinds of patients they were tried on. For some malignancies (eg, breast, non-small cell lung, and pancreas), there is a non-negligible proportion of drugs in the 5%–10% response rate interval. In testing drugs such as these on patients such as these, the designs employed should provide for early termination once inactivity is established. The distribution of response rates is quite different for adult leukemias and lymphomas, however, than for adult solid tumors. Consequently, the phase II designs appropriate in each area differ. Even for solid tumors, some of the drugs that we think of as active have pooled response rates only in the 20%–25% range.

DISCUSSION

Although the selection designs mentioned may be increasingly relevant for combinations or biologics, the objective of phase II new-agent trials has traditionally been adequate evaluation of each drug in question. Preclinical toxicology is expensive and hence it has seemed appropriate to adequately test each new agent. The number of new agents has generally been rather limited and the discovery of active drugs has not been limited by patient availability. Whitehead's design, however,

TABLE 5.—No. of drugs with specified response rate*

Disease†	% response						
	0–5	5–10	10–15	15–20	20–25	25–30	> 30
ALL	0	0	3	1	2	0	1
ANLL	6	2	3	1	4	0	1
Breast cancer	20	7	3	2	0	1	2
Colorectal cancer	32	5	3				
Head and neck cancer	13	3	2	1	3		
Hepatoma	4	0	1	0	2		
Lymphoma	2	1	2	3	2	3	7
Melanoma	19	3	3	1			
NSCLC	18	9	4	2			
Ovarian cancer	13	5	1	1	1	0	4
Pancreatic cancer	10	5	0	0	0	1	
Renal cancer	26	4					
SCLC	11	1	2	1	3	0	1

*Values = No. of drugs.

†ALL = adult acute lymphocytic leukemia; ANLL = adult acute nonlymphocytic leukemia; NSCLC = non-small cell lung cancer; and SCLC = small cell lung cancer.

TABLE 6.—Probability that observed response rate is within ± Δ of true response probability*

True response probability	No. of patients (Δ = 0.05)			No. of patients (Δ = 0.075)		
	40	80	120	40	80	120
0.05	0.82	0.96	0.99	0.98	0.99	0.99
0.10	0.68	0.86	0.93	0.88	0.97	0.99
0.15	0.60	0.78	0.87	0.80	0.94	0.98
0.20	0.55	0.73	0.83	0.75	0.90	0.96
0.25	0.52	0.69	0.79	0.71	0.87	0.94
0.30	0.50	0.66	0.76	0.69	0.85	0.92

*Values = probability.

might be appropriate for the evaluation of new agents for rare tumors.

For initial phase II testing of a new drug the optimal two-stage designs or Fleming designs seem appropriate. Although Fleming has also described designs with more than two stages, such designs are somewhat more difficult to apply in a multi-institution setting (14). After each stage one may have to suspend accrual until it is determined whether the criterion for continuing accrual is satisfied. If accrual is rapid, this can be facilitated by using a randomized phase II design.

These optimal two-stage designs or Fleming designs can effectively screen out inactive drugs while passing along for further study those drugs with at least a minimal level of activity. At least for unresponsive tumors where most of the new agents are inactive, it seems desirable to design the initial phase II trial for such screening. For such tumors, a design based on parameters $p_0 = 0.05$, $p_1 = 0.20$ or $p_0 = 0.10$, $p_1 = 0.25$ and error parameters α and $\beta \leq 0.10$ seem appropriate. β represents the probability of rejecting a drug with response probability $\geq p_1$ and this is a serious type of error. One might even argue that $\beta \leq 0.05$ should be used. α represents the probability of failing to reject a drug with response probability p_0. This is a less serious error from a drug discovery viewpoint, but it is serious from a cost perspective since traditionally most drugs have response probabilities in this range. Since a second phase II trial might be done anyhow, $\alpha = 0.10$ seems adequate. For $p_0 = 0.05$, $p_1 = 0.20$, and $\alpha = \beta = 0.10$, an optimal two-stage design requires a maximum of 37 patients with a substantial probability of early termination after 12. For $p_0 = 0.10$ or $p_1 = 0.25$, the optimal two-stage design requires a maximum of 49 patients with an 81% chance of terminating after 16 patients for drugs with true response rate of 0.05.

The designs described above serve to eliminate most of the inactive drugs. The drugs which may pass this first trial include those with low to intermediate levels of activity (eg, 5%–20%) as well as those of real interest. A trial of 35–50 patients is generally not large enough to distinguish these groups. For example, if the observed response rate is 20% (eight responses among 40 patients), the 90% confidence limit for the true response probability is about 10%–33%. Thus, the results are consistent with the drug being mediocre or very promising.

Those drugs that pass this first trial warrant further study. Although the type of further study which is appropriate will depend on the individual drug, it often seems sensible to require that, as per Gehan's original design, the amount of additional testing be that which is sufficient to estimate the true response probability with a specified precision. Table 6 indicates that for response probabilities in the range of 10%–30%, a sample size of ≥ 120 patients is required to reasonably ensure that the observed response rate is within ± 5% of the true value. A sample size of 120 patients might be viewed as three phase II studies of about 40 patients each. With 80 patients, one can be reasonably sure that the observed response rate is within ± 7.5% of the true value. Consequently, estimation of the response rate with reasonable precision for a drug passing the initial phase II trial of about 40 patients requires one to two additional trials of 40 patients. If the observed response rate after one or two trials is substantially above or below a target level of interest, fewer patients would suffice. The calculation of confidence intervals would help in this interim assessment.

For common tumors it is not impractical to require two to three phase II trials of an agent that has demonstrated activity in the initial study. There are practical reasons for wanting a second phase II trial even if the first does not demonstrate activity. There are many possible sources of variation for the results of phase II trials of the same drug against the same type of tumor. These variables include response criteria, interobserver variation in response assessment, ability to deliver planned doses, and patient selection (1,2). If data from several studies are to be pooled, however, the treatment administered, the patient populations, and the response assessments should be uniform. If there is substantial interstudy variability attributable to such causes, then estimates of the true response rate are rather meaningless and one may not be able to accomplish much more in phase II testing than to determine whether or not the drug has antitumor activity.

Although it is generally appropriate to confirm and refine indications of activity in a second phase II trial, in some cases this may not contribute substantially to the development of the drug. The role of the drug will generally be established in phase III trials with survival or disease-free survival as endpoint. The phase II evalua-

tions are for the purpose of deciding whether to conduct such phase III trials and how the regimens should be constituted. The steps in development of a drug beyond the initial phase II study that demonstrates activity are very dependent on the characteristics of the drug and the status of therapeutics for the disease where it is active. In some circumstances, initiating a phase III trial will be the most useful approach without additional phase II testing.

In this paper we have dealt with numbers of patients with a given tumor type as if all such patients were identical. This is obviously not the case. We have assumed, however, that there was a target population of such patients, probably defined based upon major prognostic factors such as prior therapy and performance status, and that the trials will include only such patients. Response rates are obviously influenced by patient characteristics. To maximize the likelihood that an active drug will not be missed, it is desirable to include only those patients who are the most likely to respond. This also minimizes the likelihood of exposing a patient unlikely to respond to a toxic agent. After a drug is determined to be sufficiently active, there may be interest in estimating its level of activity for different kinds of patients but the results should be tabulated separately. Once a drug has demonstrated meaningful antitumor activity, the degree of response, duration of response, cross-resistance characteristics, dose-response profile, pharmacokinetic characteristics, and toxicity pattern are of importance in determining how the drug will be developed.

REFERENCES

1. WITTES RE, MARSONI S, SIMON R, ET AL. The phase II trial. Cancer Treat Rep 69:1235–1239, 1985.
2. SIMON R, WITTES RE, and ELLENBERG SS. Randomized phase II clinical trials. Cancer Treat Rep 69:1375–1381, 1985.
3. GEHAN EA. The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. J Chronic Dis 13:346–353, 1961.
4. FLEMING TR. One sample multiple testing procedure for phase II clinical trials. Biometrics 38:143–151, 1982.
5. JENNISON C, and TURNBULL BW. Confidence intervals for a binomial parameter following a multi-stage test with application to MIL-STD 105D and medical trials. Technometrics 25:49–58, 1983.
6. ATKINSON EN, and BROWN BW. Confidence limits for probability of response in multi-stage phase II clinical trials. Biometrics 41:741–744, 1985.
7. CHANG M, and O'BRIEN P. Confidence intervals following group sequential tests. Controlled Clin Trials 7:18–26, 1986.
8. O'BRIEN PC, and FLEMING TR. A multiple testing procedure for clinical trials. Biometrics 35:549–556, 1979.
9. SYLVESTER RJ, and STAQUET MJ. Design of phase II clinical trials in cancer using decision theory. Cancer Treat Rep 64:519–524, 1980.
10. LEE YJ, STAQUET M, SIMON R, ET AL. Two-stage plans for patient accrual in phase II cancer clinical trials. Cancer Treat Rep 63: 1721–1726, 1979.
11. HERSON J. Predictive probability early termination plans for phase II clinical trials. Biometrics 35:775–783, 1979.
12. WHITEHEAD J. Designing phase II studies in the context of a programme of clinical research. Biometrics 41:373–384, 1985.
13. MARSONI S, HOTH D, SIMON R, ET AL. Clinical drug development: an analysis of phase II trials, 1970–1985. Cancer Treat Rep 71:71–80, 1987.
14. HERSON J. Practical side of multistage clinical trials for screening new agents. Cancer Treat Rep 67:71–75, 1983.

BRIEF REPORTS

Chemotherapy of Adult Soft Tissue Sarcoma With Combination of Doxorubicin and Methotrexate[1]

P. Presgrave,[2] R. L. Woods,[2,*] M. H. Tattersall,[3] A. S. Coates,[3] J. A. Levi,[2] R. M. Fox,[3] and D. Hedley[3]

Thirty-six adult patients with measurable advanced soft tissue sarcoma were treated with a combination of doxorubicin (70 mg/m^2) and methotrexate (50 mg/m^2) iv every 21 days. Partial remission was seen in ten of 33 evaluable patients (30%). Median duration of remission was 23 weeks, and median survival was 42 weeks. Bone marrow toxicity was the main toxic effect; 23% of the patients had a nadir leukocyte count $< 2.0 \times 10^9$/L during therapy. These results do not suggest any therapeutic advantage in adding methotrexate to doxorubicin in this context. [Cancer Treat Rep 71:1087-1088, 1987]

Both doxorubicin (1-3) and methotrexate (4,5) have been reported as active single agents in the treatment of metastatic soft tissue sarcoma. Doxorubicin is considered to be the most effective agent, with a response rate of 30% (1-3) when administered at the optimal dose of 70 mg/m^2 (6) every 21 days. Combinations containing doxorubicin have shown no definite benefit compared to doxorubicin alone. The regimen consisting of cyclophosphamide, vincristine, doxorubicin, and dacarbazine has been most widely used, and response rates of 59% have been reported (7). However, other investigators have reported lower response rates (8,9).

We report the use of a combination of doxorubicin with conventional-dose methotrexate in adult patients with advanced soft tissue sarcoma.

MATERIALS AND METHODS

Thirty-six patients with measurable advanced soft tissue sarcoma were entered in the study. Patient characteristics are described in table 1. Admission criteria included adequate bone marrow reserve (wbc count $> 3 \times 10^9$/L and platelet count $> 100 \times 10^9$/L) and adequate hepatic and renal functions (bilirubin < 30 mmol/L and serum creatinine < 160 mmol/L). No patient had received radiotherapy in the 4 weeks prior to the commencement of therapy, and none had received prior chemotherapy. All patients had a performance status of 0-3 on the Eastern Cooperative Oncology Group scale. On Day 1, patients received doxorubicin (70 mg/m^2) and methotrexate (50 mg/m^2) by iv infusion. Cycles were repeated every 3 weeks. Two cycles of therapy were given prior to assessment of response using standard World Health Organization criteria (10). Patients achieving partial remission after two courses of treatment continued on protocol therapy until they had received eight courses (ie, 560 mg of doxorubicin/m^2).

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Entered	36
Evaluable	33
Sex	
Male	19
Female	17
Histology	
Leiomyosarcoma	12
Malignant fibrous histiocytoma	5
Undifferentiated sarcoma	5
Liposarcoma	4
Synovial sarcoma	2
Fibrosarcoma	2
Mesothelioma	2
Hemangiopericytoma	2
Malignant schwannoma	1
Angiosarcoma	1
Previous therapy	
Resection of primary tumor	14
Resection with local radiotherapy	11
Biopsy alone	8
Resection of primary and secondary tumors	3

[1] Received May 4, 1987; revised July 13, 1987; accepted July 17, 1987.

[2] Department of Clinical Oncology, Royal North Shore Hospital, St. Leonards, Sydney, New South Wales, Australia.

[3] Ludwig Institute for Cancer Research, University of Sydney, New South Wales, Australia.

* *Reprint requests to:* Dr. R. L. Woods, Department of Clinical Oncology, Royal North Shore Hospital, St. Leonards, Sydney 2065, New South Wales, Australia.

RESULTS

Of the 36 patients entered in the trial, three were considered unevaluable for response after receiving one course of therapy. Two patients with stable disease withdrew with severe vomiting and mucositis. One patient died from an episode of septicemia complicating neutropenia. Ten patients (30%) achieved partial response; another five (15%) had stable disease; and 18 (55%) had disease progression during therapy. The median duration of remission was 23 weeks. Overall median survival was 42 weeks, 61 for responding patients and 21 for those with progressive disease. All patients achieving partial remission had a performance status of 0–1. The main toxic effect was myelosuppression. Eight patients (22%) had leukopenia $< 2.0 \times 10^9$ cells/L, and two had platelet count nadirs $< 50 \times 10^9$/L. Nausea and vomiting occurred in 28 patients (78%) and was severe in 16 (44%). Mucositis affected 52% of the patients, and alopecia was virtually universal.

DISCUSSION

The response rate of 30% reported in this study is similar to that achieved with single-agent doxorubicin used in comparable doses (1–3). Few trials have assessed the efficacy of doxorubicin-methotrexate drug combinations in adult soft tissue sarcoma. Bull et al (11) reported a response rate of 23% at maximum tolerated doses of both agents and a median remission duration of 35 weeks. Lowenbraun et al (12) combined doxorubicin and methotrexate in a study of soft tissue and bony sarcomas, with a response rate of 36%. Toxicity was comparable to that reported in other studies (12). Leukopenia appeared to be at least as severe as that observed during treatment with cyclophosphamide, vincristine, doxorubicin, and dacarbazine (8).

We conclude that combination chemotherapy with doxorubicin and methotrexate is moderately effective in the treatment of adult soft tissue sarcoma, particularly in patients with good performance status but is associated with significant subjective and objective toxicity. The addition of methotrexate confers no apparent therapeutic advantage over doxorubicin administered as a single agent.

REFERENCES

1. O'BRYAN RM, LUCE JK, TALLEY RW, ET AL. Phase II evaluations of Adriamycin in human neoplasia. Cancer 32:1–8, 1973.
2. BLUM RH. An overview of studies with Adriamycin (NSC-123127) in the United States. Cancer Chemother Rep Part 3, vol 6(2):247–251, 1975.
3. ROSENBAUM C, and SCHOENFELD D. Treatment of advanced soft tissue sarcomas. Proc Am Assoc Cancer Res and ASCO 18:81, 1977.
4. WILTSHAW E. Methotrexate in the treatment of sarcoma. Br Med J 2:142–145, 1967.
5. WILTSHAW E, and SUBRAMANIAN S. Chemotherapy of sarcoma. Lancet 1:683–686, 1978.
6. PINEDO HM, and KENIS Y. Chemotherapy of advanced soft tissue sarcomas in adults. Cancer Treat Rev 4:67–86, 1977.
7. GOTTLEIB JA, BAKER LH, O'BRYAN RM, ET AL. Adriamycin (NSC-123127) used alone and in combination for soft tissue and bony sarcomas. Cancer Chemother Rep Part 3, vol 6(2):271–282, 1975.
8. GIULIANO AE, LARKIN KL, EILBER FR, ET AL. Failure of combination chemotherapy (CYVADIC) in metastatic soft tissue sarcomas: implications for adjuvant studies. Proc Am Assoc Cancer Res and ASCO 19:359, 1978.
9. KARAKOUSIS CP, RAO U, and PARK HC. Combination chemotherapy (CYVADIC) in metastatic soft tissue sarcomas. Eur J Cancer 18:33–36, 1982.
10. MILLER AB, HOOGSTRATEN B, STAQUET M, ET AL. Reporting results of cancer treatment. Cancer 47:207–214, 1981.
11. BULL FE, IRWIN LE, PUGH RP, ET AL. Phase I study of Adriamycin/methotrexate combinations in sarcoma. Proc Am Assoc Cancer Res and ASCO 17:50, 1976.
12. LOWENBRAUN S, MOFFITT S, SMALLEY R, ET AL. Combination chemotherapy with Adriamycin, cyclophosphamide, and methotrexate in metastatic sarcoma. Proc Am Assoc Cancer Res and ASCO 18:80, 1977.

BRIEF REPORTS

Inhibitory Action of Flurbiprofen and Mopidamole on Tumor Lung Metastasis Formation in Mice[1]

A. Mamytbeková,* K. Řežábek, J. Grimová, and J. Svobodová[2,3]

Flurbiprofen, 0.25 mg/kg, administered to mice orally once daily during 3 days prior to an iv transplantation of Lewis lung carcinoma cells, protected 50%–57% of experimental animals from the formation of lung tumor colonies. With the daily dose of 1.0 mg/kg, this effect was less pronounced. Mopidamole, twice daily 90 mg/kg orally during 3 days, did not have this effect. [Cancer Treat Rep 71:1089–1090, 1987]

Many authors support the concept that blood platelets play an important role in tumor hematogenous metastasizing through enhancing tumor cell adhesion to endothelium and through protecting tumor cells from destruction by the cellular immune system. Many investigators have tried to prevent metastasis with anticoagulants and antiaggregating agents (1). In the present study, we have examined the effect of two platelet function inhibitors—flurbiprofen and mopidamole—on the formation of artificial metastases.

MATERIALS AND METHODS

Male C57BL/6 mice (20–22 g) were used throughout the experiments. Flurbiprofen (Flugalin tablets, Galenika, Belgrad, Yugoslavia) or mopidamole (Res Inst Pharm Biochem, Prague, Czechoslovakia) were suspended in 10 ml/kg of water and administered to experimental animals into the stomach with a gavage as given in table 1. The tumor used was Lewis lung carcinoma (LLC) as described previously (2). Suspensions of tumor cells were prepared according to Maat (3), and 1×10^6 viable tumor cells per mouse were introduced iv. The animals were killed on Day 15 after tumor transplantation, and the tumor colonies visible on the lung surface were evaluated.

RESULTS

In the untreated control group, the percentage of animals with lung tumor nodules ranged from 92% to 100% (table 1). After 3 days of pretreatment with flurbiprofen in the daily oral dose of 0.25 mg/kg, the number of animals with lung tumor nodules decreased by 50% and 57%. A similar pretreatment with the daily dose of 1.0 mg/kg showed but an insignificant antimetastatic effect. This effect was not observed after the pretreatment with flurbiprofen in a single oral dose of 0.25 mg/kg given before the tumor transplantation.

Mopidamole administered orally prior to the iv transplantation of tumor cells did not inhibit subsequent lung tumor colony formation.

In a combination therapy with flurbiprofen, 0.25 mg/kg, plus mopidamole, 90 mg/kg, twice daily during 3 days prior to the iv transplantation of tumor cells, the number of animals with lung tumor nodules decreased by 46%. This effect was not seen after the combination of flurbiprofen and mopidamole given only once on the day of the iv transplantation of tumor cells.

DISCUSSION

The present study shows that flurbiprofen, administered to mice at the repeated dose of 0.25 mg/kg, protected 50% to 57% of the experimental animals from the formation of tumor metastatic nodules in the lungs. With a higher dose of 1.0 mg/kg this effect was less pronounced.

Similar effects were seen in our previous experiments with spontaneously metastasizing LLC, transplanted im and excised after 6 days. Here, flurbiprofen administered during 8 days at the daily dose of 0.25 mg/kg protected seven of 12 animals (58%) from lung metastases,

[1] Received Dec 29, 1986; revised July 21, 1987; accepted Aug 3, 1987.

[2] Research Institute for Pharmacy and Biochemistry, Prague, Czechoslovakia.

[3] We thank ing. Hondlik for useful advice in the statistical treatment of the data.

* *Reprint requests to:* Dr. A. Mamytbeková, Research Institute for Pharmacy and Biochemistry, 17 Kourimská, CS-13060, Prague, Czechoslovakia.

TABLE 1.—Effects of flurbiprofen, mopidamole, and their combination on tumorous lung nodule occurrence after iv transplantation of LLC cells

Compound	Dose (mg/kg/day)	Treatment schedule (days)*	Animals with lung tumorous nodules	
			Counts†	%‡
Control; water	10 ml/kg	−2, −1, 0	15/15	100 (78; 100)
Flurbiprofen	0.25	−2, −1, 0	6/14	43 (18; 71)§
Flurbiprofen	1.00	−2, −1, 0	16/18	89 (65; 99)
Control; water	10 ml/kg	−2, −1, 0	11/12	92 (62; 100)
Flurbiprofen	0.25	−2, −1, 0	6/13	46 (19; 75)§
Mopidamole	2 × 90.0	−2, −1, 0	11/13	85 (55; 98)
Flurbiprofen + Mopidamole	0.25 + 2 × 90.0	−2, −1, 0	7/14	50 (23; 77)
Control; water	10 ml/kg	0	11/11	100 (72; 100)
Flurbiprofen	0.25	0	11/12	92 (62; 100)
Mopidamole	2 × 90.0	0	14/14	100 (77; 100)
Flurbiprofen + Mopidamole	0.25 + 2 × 90.0	0	13/14	93 (66; 100)

*0 = day of tumor cell transplantation.

†No. of animals with any tumorous nodules visible on the lung surface/total No. in group. Values were determined at death on Day 15 after tumor transplantation.

‡% of animals with any tumorous nodules on lung surface; parentheses indicate 95% confidence limits.

§Significantly different from controls ($P = 0.05$, Fisher's exact probability test).

while at the daily dose of 1.0 mg/kg only two of ten animals (20%) were protected (2).

In the experiments described by Hellman and Pym (4), after the maximum tolerated doses of flurbiprofen (up to 4.0 mg/kg twice daily) had been administered, the formation of lung metastases in mice was not affected.

To explain the observed effects of higher and lower doses of flurbiprofen, we propose a working hypothesis that flurbiprofen, a cyclooxygenase inhibitor, at the lower doses influences the relation between the synthesis of the platelet aggregation-inducing agent thromboxan and the synthesis of the platelet aggregation-opposing agent prostacyclin in favor of the synthesis of prostacyclin (5). As far as higher doses of flurbiprofen are concerned, we assume that they impair the synthesis of both the prostaglandin derivatives, and so the protective antimetastatic action gets lost. The proof of this hypothesis remains to be given by further studies. An analogous explanation was given for the varying contradictory effects of low and high aspirin doses (5,6).

REFERENCES

1. KARPATKIN S, and PEARSTEIN E. Role of platelets in tumor cell metastasis. Ann Intern Med 95:636-641, 1981.
2. MAMYTBEKOVA A, ŘEŽABEK K, KACEROVSKA H, ET AL. Antimetastatic effect of flurbiprofen and other platelet aggregation inhibitors on metastases formation in mice. Neoplasma 33:417-421, 1986.
3. MAAT B. Extra pulmonary colony formation after intravenous injection of tumor cells into heparin-treated animals. Br J Cancer 37: 369-376, 1978.
4. HELLMAN K, and PYM B. Antitumor activity of flurbiprofen in vivo and in vitro. *In* Prostaglandins and Cancer: First International Conference (Powles T, et al, eds). New York, Alan R. Liss, 1982, pp 767-774.
5. HONN K, BUSSE WD, and SLOANE BF. Prostacyclin and thromboxanes. Implications for their role in tumor cell metastasis. Biochem Pharmacol 32:1-11, 1983.
6. VERSTRAETE M, and KIENAST J. Pharmacology of the interaction between platelets and vessel wall. Clin Haematol 15:493-507, 1986.

BRIEF REPORTS

Oral Gestrinone: A Novel Antiprogestin With No Antitumor Activity in Endocrine-Sensitive Breast Cancer[1]

David Cunningham,[2] Jean-Claude Gazet,[2] Hubert T. Ford,[2] and R. Charles Coombes[2,3,*]

We have treated 15 patients with locally advanced or metastatic breast cancer using the synthetic 19-norsteroid gestrinone (2.5 mg orally every 3 days). All patients had assessable disease and endocrine-sensitive tumors, as defined by a previous positive response to endocrine therapy. There were no objective responses. Six patients had disease stabilization and nine had progressive disease on treatment. Seven patients were given endocrine therapy after gestrinone and three have responded. Gestrinone has no significant antitumor activity in hormone-sensitive breast cancer. This, however, does not preclude its use in benign breast disease, particularly since other agents used for benign breast disease can mask occult primary carcinoma. [Cancer Treat Rep 71:1091-1092, 1987]

Gestrinone is a synthetic 19-norsteroid that was originally developed as an oral contraceptive for women (1,2). Its use as a contraceptive was abandoned for several reasons, including the development of breast atrophy in up to 40% of patients (1,2). However, in view of this side effect, its potential application in the treatment of benign breast disease was recognized and is being evaluated by this group.

In premenopausal patients with benign breast disease, gestrinone has several possible mechanisms of action. It can suppress gonadotropin release by the pituitary (3) and, while binding to the progesterone receptor (PR) (4), is also a potent antiprogesterone agent. It has weak affinity for both the androgen and mineralocorticoid receptors but none for the estrogen receptor (ER) (5). In postmenopausal women, it is likely that the compound exerts its effects by its antiprogesterone action (5). Since it is well established that most breast cancers containing ER also possess PR (6), it was possible that gestrinone might have antitumor activity against this subset of endocrine-sensitive breast cancer. Furthermore, the study of Kelly et al (7) showed a progressive inhibition of rat mammary tumor development in rats given gestrinone. For this reason, we initiated a study of gestrinone in patients with breast cancer.

PATIENTS AND METHODS

We treated 15 female patients (mean age, 72.1 yrs; range, 50–87) with histologically confirmed locally advanced or metastatic breast cancer. All were naturally postmenopausal and had assessable disease as defined by the International Union Against Cancer (8). The sites of disease were bone (ten), liver (two), lung (three), and soft tissue (13). All patients had already received at least a single trial of endocrine therapy and had responded. An additional seven patients had received a second endocrine agent; three of these had responded and four had stable disease. Details of endocrine treatment are shown in table 1. No patient had been treated with a progesterone. One patient had been given chemotherapy. None had received any form of therapy for the 4 weeks prior to the start of treatment with gestrinone.

Disease was fully staged before the start of therapy and every 3 months during treatment, with clinical examination, chest radiograph, limited skeletal survey, liver ultrasound, isotope bone scan, cbc, liver function tests, and determination of gamma glutamyl transpeptidase, calcium, phosphate, urea, and electrolyte levels. Clinical examination, biochemistry, and toxicity assessment were repeated every 4 weeks. The ER content of

[1] Received Apr 20, 1987; revised Aug 4, 1987; accepted Aug 11, 1987.
[2] St. George's Hospital, London, England.
[3] Ludwig Institute for Cancer Research (London-St. George's Group), St. George's Hospital Medical School, London, England.

* *Reprint requests to:* Dr. R. C. Coombes, Ludwig Institute for Cancer Research (London-St. George's Group), St. George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, England.

TABLE 1.—Details of previous endocrine therapy

Therapy	Total No. of patients	Response	
		Partial response	Stable disease
1st-line			
Tamoxifen	9	8	1
4-Hydroxyandrostenedione	4	2	2
Aminoglutethimide	1	1	—
TAD*	1	1	—
2nd-line			
4-Hydroxyandrostenedione	6	2	4
Tamoxifen	1	1	—

*Tamoxifen, aminoglutethimide, and danazol.

the tumor was measured in 11 of 15 patients by a modification of the method of McGuire et al (9), and all 11 patients had ER-positive tumors. Response to treatment was assessed according to standard criteria of the International Union Against Cancer (8). All patients gave full informed consent, and the protocol was approved by the St. George's Hospital Ethical Committee.

Gestrinone was given at a dose of 2.5 mg orally every 3 days.

RESULTS

All patients received ≥ 4 weeks of treatment (median, 7.5; range, 4–24). Nine patients failed to respond. Five patients had disease stabilization (median, 6 mos; range, 6–8); one of these patients had treatment discontinued because of toxicity. Eleven patients had no side effects. Two patients developed mild ankle swelling; one patient developed vaginal bleeding, and one had superficial thrombophlebitis. No patient developed any abnormality of serum urea and electrolyte levels, liver function, or cbc.

Seven patients received endocrine treatment after gestrinone. Three of these patients responded (two given medroxyprogesterone acetate and one given high-dose tamoxifen), and in one patient, the disease stabilized. Two patients failed to respond, and it is too early to assess the response in one.

DISCUSSION

Gestrinone had no significant antitumor activity in this group of patients with locally advanced or metastatic breast cancer. Patients were selected on the basis of favorable response to previous endocrine therapy, creating optimal circumstances for the detection of a new active endocrine agent. It therefore is disappointing that this compound, the first antiprogesterone to be tested in patients with breast cancer, was ineffective when used as a single agent. A possible explanation is that insufficient gestrinone was administered to bind with available PR. Also, in the absence of data on the PR content of the tumors treated, it is conceivable that many of these tumors had become progesterone negative after previous endocrine therapy. Thus, it could be argued that gestrinone was inadequately tested. However, the response of three of the seven patients treated with endocrine therapy subsequent to gestrinone, including two given medroxyprogesterone acetate, tends to mitigate against this possibility.

Nevertheless, the lack of activity of gestrinone in breast cancer may be of considerable clinical advantage in the context of the treatment of benign breast disease. One of the major concerns about the current treatment of benign breast disease with such agents as tamoxifen or danazol (10,11) is that endocrine-sensitive breast cancer will regress on these therapies. On the basis of our results, this is unlikely to occur with gestrinone. Also, although 27% of the patients experienced toxicity with the dosage of gestrinone used in this study, our experience with a lower dosage in benign breast disease (2.5 mg twice weekly) revealed a reduction in the incidence of side effects.

Thus, gestrinone is inactive in the treatment of breast cancer, but this lack of activity may be of value when it is used to treat benign breast disease.

REFERENCES

1. SAKIZ E, AZADIAN-BOULANGER G, LARAQUE G, ET AL. A new approach to estrogen-free contraception based on progesterone receptor blockage by mid-cycle administration of ethyl norgestrinone (R2323). Contraception 10:467, 1974.
2. MORA G, FAUNDES A, and PATORE V. Clinical evaluation of an oral progestin contraceptive R2323, 5 mg administered at weekly intervals. Contraception 10:145, 1974.
3. PROULX L, LABRIE F, VEILEUX R, ET AL. Actions of progestin and androgens at the hypothalamo-adenohypophyseal level in female rat. *In* Medical Management of Endometriosis (Raynaud J-P, Ojasoo T, and Martini L, eds). New York, Raven Press, 1984, p 149.
4. MOGUILEWSKY M, and PHILIBERT D. Dynamics of the receptor interactions of danazol and gestrinone in the rat: correlation with biological activities. *In* Medical Management of Endometriosis (Raynaud J-P, Ojasoo T, and Martini L, eds). New York, Raven Press, 1984, p 163.
5. RAYNAUD J-P, and OJASOO T. The design and use of sex-steroid antagonists. J Steroid Biochem 25:811, 1986.
6. MCGUIRE WL. Steroid receptors in clinical breast cancer. *In* Perspectives in Steroid Receptor Research (Bresciani F, ed). New York, Raven Press, 1980, p 239.
7. KELLY PA, ASSELIN J, TURCOT-LEMAY L, ET AL. Effects of progesterone and R2323 on the development of dimethylbenzanthracene-induced mammary tumors. Eur J Cancer Clin Oncol 15:1243, 1979.
8. HAYWARD JL, CARBONE PP, HEUSEN JC, ET AL. Assessment of response to therapy in advanced breast cancer. A project of the programme on clinical oncology of the International Union Against Cancer, Geneva, Switzerland. Br J Cancer 35:292–298, 1977.
9. MCGUIRE WL, and DE LA GARZA M. Improved sensitivity in the measurement of estrogen receptor in human breast cancer. J Clin Endocrinol Metab 37:986–989, 1973.
10. FENTIMAN IS, CALEFFI M, BRAME K, ET AL. Double-blind controlled trial of tamoxifen therapy for mastalgia. Lancet 1:287, 1986.
11. EGGERT-KRUSE W, VON FOURNIER D, LEGLER U, ET AL. Comparison of danazol with tamoxifen, gestagen, acupuncture, local treatment and placebo: results in 1000 patients. *In* Benign Breast Disease (Baum M, George WD, and Hughes LE, eds). London, Royal Society of Medicine, 1984, pp 99–102.

BRIEF REPORTS

Facilitation of Emergence of Multidrug-Resistant State by Alteration of Tumor Environment: Implications From Competitive Ecology Models[1,2]

Seth Michelson[3,*]

The presence of multidrug-resistant (MDR) cells in a solid tumor constitutes a major problem in cancer therapy. Current thinking suggests that the resistant phenotype arises de novo during the tumor's evolution via somatic mutation mechanisms. The proportion of MDR cells, once established, may be enriched during therapy as a consequence of differential cell kill. Michelson et al have developed mathematical models of these phenomena to gain an insight into the dynamics of clonal subpopulation emergence in general and MDR emergence in particular, and I now show that one unexpected consequence of therapy may be the facilitation of MDR emergence due to damage inflicted on the host. The therapeutic damage to the host is modeled as a decreased ability to carry a specific tumor burden. [Cancer Treat Rep 71:1093-1094, 1987]

Michelson et al (1) have developed three deterministic mathematical models to describe dynamics of tumor cells in a heterogeneous microenvironment. We found that one consequence of therapy is that any change in the cellular microenvironment that induces a decrease in the host's ability to carry the tumor (eg, disruption of tumor microvasculature) results in new and fundamentally different neoplastic population dynamics. Because of this, emergence of nascent multidrug-resistant (MDR) subpopulations (2-4) could be facilitated. Due to the importance of the MDR phenotype in the design of therapeutic protocols, I concentrate on this phenomenon. However, other types of emergence phenomena can also be modeled by the general equations shown here.

MODELS AND EQUILIBRIA

Michelson et al (1) have shown that for a tumor composed of distinct subpopulations competing for limited resources, growth can be modeled by a system of equations that describe dynamic interactions involving both intraspecific and interspecific parameters. In this regard, the classical competition model for two distinct (tumor) populations is given by Waltman (5):

$$x' = rx(1 - x/N - ay) \qquad [1]$$
$$y' = sy(1 - y/M - bx),$$

where $'$ = rate change per unit of time; r and s = the individual Malthusian growth rates; N and M = the individual carrying capacities of the environment for the x and y cells, respectively; and a and b = the interspecific weights of competition for one population or the other. This model allows the tumor to grow so that either population can become extinct (competitive exclusion) or an equilibrium mix is achieved. The products aN and bM determine which outcome will obtain. If aN is ≤ 1 and bM is ≥ 1, the y population will be excluded, and the reverse situation is also true. If both products are > 1, which population is excluded depends on the initial mix of the tumor. Only when both products are < 1 can equilibrium be attained, and the ultimate equilibrium mix is the solution of:

$$x + aNy = N \qquad [2]$$
$$y + bMx = M.$$

These theoretical results can be used to gain insight into the emergence dynamics of MDR. However, using deterministic systems to describe an essentially stochastic process requires that behavior be described only as an "average" response. In other words, one cannot predict a single case of emergence but only the average behavior of tumor cells over all emergent events. How-

[1] Received May 11, 1987; revised Aug 10, 1987; accepted Aug 17, 1987.
[2] Supported by American Cancer Society grant IN-45Z from Brown University.
[3] Department of Radiation Medicine and Biology Research, Rhode Island Hospital, and Department of Radiation Medicine, Brown University, Providence.
* *Reprint requests to:* Seth Michelson, PhD, Department of Radiation Medicine and Biology Research, Rhode Island Hospital, 593 Eddy St, Providence, RI 02903.

ever, in large populations, the average behavior can still provide us with an insight into the expected dynamics of the average tumor.

Goldie and Coldman (6) and Coldman et al (7) suggest that the underlying mutation rate for the emergence of MDR is on the order of one viable mutation in 10^6 mitoses. Therefore, the probability of at least one emergence event occurring in a tumor containing 10^6 cells is approximately 0.63. However, if it is assumed that resistant cells (eg, y cells) emerge from sensitive cells (x cells) and that resistant cells have growth dynamics such that either bM is > 1 or both aN and bM are > 1, *the emergent population, on the average, will be excluded before it can establish itself.* Only when the resistant population competes equally with the sensitive population can the new population emerge.

Leith et al (8) have shown that the total tumor volume the host can carry (carrying capacity) can be reduced when a heterogeneous human adenocarcinoma of the colon (DLD-1) is treated with mitomycin. Michelson et al (submitted for publication) have analyzed these dynamics in detail. Importantly, if a cytotoxic agent impairs the host's ability to carry the tumor, then *the repopulation dynamics in the treated tumor are actually governed by two new asymptotic carrying capacities.* Leith et al report that the new carrying capacities (average of ten to 12 tumors) are approximately 30% of the original values. If each population still competes for resources with the same effectiveness as before (ie, a and b are not affected by the agent), a new equilibrium mix can be established [ie, both a(0.3N) and b(0.3M) may be < 1]. Even if the original growth dynamics were such that MDR emergence in the normal tumor was ruled out, this new parameterization could result in the two populations attaining asymptotic equilibrium. For example, if $N = 6500$ mm^3, $M = 7000$ mm^3, $a = 1.2 \times 10^{-4}$, and $b = 1.6 \times 10^{-4}$, then the y population will be excluded. If we decrease both N and M by a factor of 0.3, solving equation 2 shows that the new ecology will achieve an end-equilibrium mix of 50:50.

If MDR can also be induced by drug administration, then the simplest model that describes these dynamics can be formulated as in equation 1:

$$x' = rx(1 - x/N - ay) - px \qquad [3]$$
$$y' = sy(1 - y/M - bx) + qx,$$

where p = a loss function from the sensitive population and q = the induction rate to resistance. Each is a positive constant in the presence of drug. If a tumor is initially sensitive, therapy results in the removal of some x cells due to cell kill and some due to influx into the y population. Therefore, p is $\geq$ q. Even if the competitive dynamics of the original system were such that resistant y cells arising at random had been competitively excluded, drug toxicity that decreases the ultimate carrying capacity of the environment of the tumor could result in new equilibrium dynamics.

Certainly, more sophisticated models for the induction of MDR are possible. For example, if emergence is a function of drug concentration in the tumor milieu, the transition rates p and q are not constant, but time-dependent functions. The equilibrium dynamics for these more sophisticated models cannot be specified as simple closed form solutions and require numerical simulation.

These preliminary results are based on theoretical conjecture that depends explicitly on a number of assumptions. The first assumption is that these models correctly describe the microecologies in which heterogeneous tumors evolve. It is assumed that host damage induced by therapy is permanent. In the data presented by Leith et al (8), the in vivo effects of single doses of mitomycin were followed for approximately 1 month, and the data obtained were used to derive parameter estimates for the carrying capacities in these mathematical models. If the environment is resilient, ie, if the host can repair some fraction of the damage, then the extrapolated carrying capacities for the tumor derived from short-term data may be misleading; ie, the environment itself may be changing, and effects on long-term neoplastic growth cannot be quantitatively predicted.

It is also assumed that damage to the host results in effects that do not distinguish one population from the other. This may not be the case. If populations compete for a limited number of overlapping resources, then toxicity may result in differential effects on competition rates a and b. Therefore, therapy could result in unexpected neoplastic population dynamics, and these new dynamics could facilitate the emergence and establishment of an MDR subpopulation.

REFERENCES

1. MICHELSON S, MILLER BE, GLICKSMAN AS, ET AL. Tumor microecology and competitive interactions. J Theor Biol, 1987. In press.
2. JULIANO RL, and LING VA. A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. Biochim Biophys Acta 455:152–162, 1976.
3. LING V, KARTNER N, SODO T, ET AL. Multidrug-resistance phenotype in Chinese hamster ovary cells. Cancer Treat Rep 67:869–874, 1983.
4. CURT GA, CLENDENINN NJ, and CHABNER BA. Drug resistance in cancer. Cancer Treat Rep 68:87–99, 1984.
5. WALTMAN P. Competition Models in Population Biology. Society for Industrial and Applied Mathematics, vol 45, 1983.
6. GOLDIE JH, and COLDMAN AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep 63:1727–1731, 1979.
7. COLDMAN AJ, GOLDIE JH, and NG V. The effect of cellular differentiation on the development of permanent drug resistance. Math Biosci 74:177–198, 1985.
8. LEITH JT, FAULKNER LE, BLIVEN SF, ET AL. Compositional stability of artificial heterogeneous tumors in vivo: use of mitomycin C as a cytotoxic probe. Proc Am Assoc Cancer Res 28:45, 1987.

Phase II Trial of Diaziquone in Patients With Refractory and Relapsing Multiple Myeloma: A Southwest Oncology Group Study[1,2]

W. J. Stuckey,[3] John Crowley,[4] Laurence H. Baker,[5] Nye R. Larrimer,[6] Karl H. Hanson,[7] John D. Bonnet,[8] and Leonard A. White, Jr[9,*]

Patients with multiple myeloma refractory to drug combinations containing a corticosteroid, alkylating agent, vincristine and/or doxorubicin have a poor prognosis, with a median survival < 12 months. Diaziquone (AZQ) is a synthetic benzoquinone that showed antitumor activity in experimental tumor systems and is thought to exhibit alkylating activity (1). Because of the known activity of various alkylating agents in myeloma, the Southwest Oncology Group (SWOG) performed a phase II study of AZQ in patients with refractory myeloma.

Patients with multiple myeloma refractory to or relapsing from previous therapy were eligible for this study. Patients were required to have serum creatinine ≤ 2.0 mg/dl; serum bilirubin ≤ 2.0 mg/dl; and measurable serum and/or urine M component or easily measurable plasmacytoma; be at least partially ambulatory; and have no evidence of bone marrow depression from prior chemotherapy or irradiation. Informed consent was obtained in accordance with federal and institutional guidelines.

AZQ was administered as an infusion over 30 minutes at a starting dose of 10 mg/m^2 weekly for four doses, which composed one course, followed by a 2-week rest period (2). Blood cell counts were monitored weekly and serum liver function tests, creatinine, calcium, and serum/urine M component were repeated at 6-week intervals.

Characteristics of the 36 patients entered in this study are shown in table 1. Nineteen patients received eight or more doses in two or more courses and were observed ≥ 10 weeks.

The major toxicity, myelosuppression, was quite variable. Thirteen of 35 patients had severe or life-threatening thrombocytopenia while 13 of 35 experienced mild or no thrombocytopenia. Eight of 35 patients had severe

TABLE 1.—Patient characteristics

Characteristic	No. of patients (%)
Entered (1 patient received no AZQ)	36 (100)
Evaluable for toxicity	35 (97)
Evaluable for response	32 (89)
Sex	
Female	15 (43)
Male	20 (57)
Median age in yrs (range): 65 (43–75)	
Prior chemotherapy*	
VMCP/VBAP	16 (46)
MP	10 (29)
VMCP	5 (14)
Other	4 (11)
Stage of disease	
Relapsing	25 (69)
Refractory	11 (31)
No. of courses of AZQ	
< 2	16 (46)
2	9 (26)
≤ 3	6 (17)
> 3	4 (11)
Response	
Partial	1 (3)
Disease improvement	2 (6)
Stable disease	17 (53)
Disease progression	12 (38)
Toxicity	
Thrombocytopenia	
Severe	10
Life-threatening	3
Neutropenia	
Severe	7
Life-threatening	1
Nausea/vomiting	
Severe	1/1
Life-threatening	0/0

*V = vincristine; M = melphalan; C = cyclophosphamide; P = prednisone; B = carmustine; and A = doxorubicin.

[1] Received Mar 30, 1987; revised June 29, 1987; accepted July 8, 1987.
[2] Supported in part by Public Health Service grants CA-03389, CA-37429, CA-35261, CA-35438, CA-28862, CA-35128, CA-04919, CA-16385, CA- 21116, CA-22433, CA-35158, CA-35090, CA-35262, CA-35281, and CA-32102 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.
[3] Tulane University Medical Center, New Orleans, LA.
[4] Southwest Oncology Group Biostatistical Center, Seattle, WA.
[5] Wayne State University Medical Center, Detroit, MI.
[6] Columbus CCOP, OH.
[7] Midwest CCOP, Kansas City, MO.
[8] Scott and White Clinic, Temple, TX.
[9] St. Louis CCOP, MO.

* *Reprint requests to:* Southwest Oncology Group (SWOG-8310), Operations Office, 5430 Fredericksburg Rd, Suite 618, San Antonio, TX 78229.

or life-threatening neutropenia, while 20 patients experienced mild or no neutropenia. Hematological toxicity was not cumulative.

Response to therapy was evaluated by Chronic Leukemia-Myeloma Task Force criteria (3). One patient responded transiently, two improved, 17 remained stable, and 12 had disease progression. Median survival was 8.1 months.

AZQ administered by iv bolus in this schedule as well as that of Vinciguerra et al (4) does not appear to be promising in the treatment of myeloma. If additional studies of AZQ are conducted in myeloma, a prolonged infusion should be considered, as this schedule appears to be more active in leukemia (5).

REFERENCES

1. DRISCOLL JS, DUDECK L, CONGLETON G, ET AL. Potential CNS antitumor agents VI. Aziridinylbenzoquinones III. J Pharm Sci 68: 185–188, 1979.
2. BAKER L, SAMSON M, LEICHMAN C, ET AL. Phase I evaluation of aziridinylbenzoquinone in a weekly iv schedule. Proc Am Assoc Cancer Res and ASCO 22:189, 1981.
3. COMMITTEE OF THE CHRONIC LEUKEMIA-MYELOMA TASK FORCE, NATIONAL CANCER INSTITUTE. Proposed guidelines for protocol studies. II. Plasma cell myeloma. Cancer Chemother Rep Part 3, vol 4(1):145–158, 1973.
4. VINCIGUERRA V, ANDERSON K, and MCINTYRE OR. Diaziquone for resistant multiple myeloma. Cancer Treat Rep 69:331–332, 1985.
5. LEE EJ, VAN ECHO DA, EGORIN MJ, ET AL. Diaziquone given as a continuous infusion is an active agent for relapsed adult acute nonlymphocytic leukemia. Blood 67:182–187, 1986.

Phase II Study of Isotretinoin in the Treatment of Advanced Non-Small Cell Lung Cancer[1,2]

Steven M. Grunberg[3,*] and Loretta M. Itri[4,5]

Several human epidemiologic studies have suggested a relationship between low vitamin A intake or serum levels and lung cancer (1). Clinical and pathologic reversal of leukoplakia (2) and bronchial squamous metaplasia (3) by retinoids has been successfully accomplished. In addition, clinical response of squamous cancers (4) and chronic myelomonocytic leukemia (5) has been described. Isotretinoin is a retinoid that is not transported by retinol-binding protein. Dose-limiting hepatotoxicity is therefore delayed, allowing use of higher doses (5). We examined the activity of isotretinoin at maximal doses against advanced non-small cell lung cancer.

Adults with measurable or evaluable unresectable non-small cell lung cancer were eligible. Life expectancy > 4 months; Karnofsky performance status $\geq 60\%$; and adequate hematologic, renal, and hepatic reserve were required. Baseline fasting serum triglyceride $> 2 \times$ normal or recent ingestion of megadose vitamins made a patient ineligible. Patients received isotretinoin at 100 mg/m^2 orally every day, with the daily dose approximated to the closest number of 40-mg tablets. If subjectively intolerable mucocutaneous toxicity or headache, fasting hypertriglyceridemia > 500 mg/100 ml, or significant hepatotoxicity (SGOT $> 3 \times$ normal) appeared, treatment was withheld until resolution and resumed at a dose decreased by one tablet per day.

Twenty-five patients were entered, of whom 23 are evaluable. One inevaluable patient with a significant cardiac history had a myocardial infarction and one patient was lost to follow-up. Analysis was performed on the 23 evaluable patients described in table 1. The absolute median starting daily dose of isotretinoin was 200 mg (range, 160–240). Patients were treated for a

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Entered	25
Evaluable	23
Male/female	18/5
Median age in yrs (range): 63 (42–78)	
Median Karnofsky performance status (range): 80% (60%–100%)	
Histology	
Adenocarcinoma	15
Squamous cell carcinoma	7
Large cell carcinoma	1
Prior therapy	
Surgery alone	1
Radiotherapy alone	2
Chemotherapy alone	1
Surgery/radiotherapy	1
Surgery/chemotherapy	5
Radiotherapy/chemotherapy	4
Surgery/radiotherapy/chemotherapy	2
None	7
Median duration of treatment in wks (range): 6 (1–25)	
Best response	
Complete	0
Partial	1 (25 wks)
Stable disease	5 (6, 8, 9, 9, 11 wks)
Progressive disease	17
Toxicity (requiring dose modification)	
Dry skin	19 (1)
Xerostomia	8 (1)
Conjunctivitis	12 (0)
Hypertriglyceridemia	6 (2)
Headache	2 (1)
Elevated transaminase	1 (0)

[1] Received Apr 28, 1987; revised July 8, 1987; accepted July 16, 1987.
[2] Supported in part by Public Health Service grants CA-14089 and CA-37419 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.
[3] Division of Medical Oncology, University of Southern California Comprehensive Cancer Center, and Los Angeles County-University of Southern California Medical Center, Los Angeles.
[4] Department of Medical Research, Hoffmann-La Roche Inc, Nutley, NJ.
[5] We thank the San Gabriel Valley Community Clinical Oncology Program for assistance with patient accrual and Sandra Cowthran for secretarial assistance.

Reprint requests to: Steven M. Grunberg, MD, Divison of Medical Oncology, University of Southern California Comprehensive Cancer Center, 2025 Zonal Ave, GH 10-436, Los Angeles, CA 90033.

median of 6 weeks (range, 1-25). Twenty of the 23 patients were treated for at least 4 weeks.

No patient achieved complete response. Partial response was noted in one patient with previously untreated adenocarcinoma of the lung in whom significant regression of pulmonary disease developed within 2 months and was maintained for almost 6 months.

Therapy was generally well-tolerated. Dry skin with peeling developed in 19 patients but resolved within 4 weeks of termination of therapy. Dry skin, xerostomia, and conjunctivitis could be controlled with local measures. In the patient who received an extended course of therapy, skin changes resolved spontaneously in 2-3 months without any change or interruption of therapy. Hypertriglyceridemia (fasting serum triglyceride > 200 mg/100 ml) was seen in six patients, with two patients requiring dose reduction.

In a broad phase II study of isotretinoin, Meyskens et al (4) described mixed response in two of eight patients with squamous cell lung cancer. The encouraging preliminary results in preneoplastic and neoplastic lung lesions led to this trial. The maximum tolerated dose of 100 mg/m^2 has been previously defined (5) and was the dose used. However, only one of 23 evaluable patients (4%) responded to treatment. Although retinoids may have value as chemopreventive agents, activity of oral isotretinoin in advanced non-small cell lung cancer appears to be minimal.

REFERENCES

1. CLAMON GH. Retinoids for the prevention of epithelial cancers: current status and future potential. Med Pediatr Oncol 8:177-185, 1980.
2. HONG WK, ENDICOTT J, ITRI LM, ET AL. 13-*cis*-Retinoic acid in the treatment of oral leukoplakia. N Engl J Med 315:1501-1505, 1986.
3. MISSET JL, SANTELLI G, HOMASSON JP, ET AL. Regression of bronchial epidermoid metaplasia in heavy smokers with etretinate treatment. Cancer Detect Prev 9:167-170, 1986.
4. MEYSKENS FL, JR, GILMARTIN E, ALBERTS DS, ET AL. Activity of isotretinoin against squamous cell cancers and preneoplastic lesions. Cancer Treat Rep 66:1315-1319, 1982.
5. GOLD EJ, MERTELSMANN RH, ITRI LM, ET AL. Phase I clinical trial of 13-*cis*-retinoic acid in myelodysplastic syndromes. Cancer Treat Rep 67:981-986, 1983.

Phase II Study of Caracemide in Advanced or Recurrent Non-Small Cell Lung Cancer[1,2]

Chandra P. Belani,* Mario Eisenberger, David Van Echo, Deborah Hiponia, and Joseph Aisner[3]

The role of chemotherapy for patients with advanced or recurrent non-small cell lung carcinoma remains unestablished (1,2). The identification and development of new chemotherapeutic agents and new modalities of therapy are essential for further progress in the treatment of this disease.

Caracemide has demonstrated activity against tumor xenografts and ip murine P388 leukemia cells (3). The mechanism of action of this drug is unknown. It appears to be a nonspecific inhibitor of macromolecular synthesis. Phase I studies have indicated that treatment by 5-day continuous infusion was well-tolerated, with dose-limiting neurological toxic effects such as depression, lethargy, confusion, and dementia associated with electroencephalogram abnormalities (4). The recommended phase II dose of 650 mg/m^2 daily by continuous infusion over 5 days was associated with minimal toxicity. Our results in the treatment of non-small cell lung cancer are reported herein.

MATERIALS AND METHODS

Eighteen patients with histologically confirmed unresectable or recurrent non-small cell lung carcinoma were entered. Patients were eligible if they had measurable disease; performance status $\geq$ 70% (Karnofsky scale); no prior chemotherapy; adequate bone marrow reserve defined as wbc count $>$ 3500/μl; platelet count $>$ 100,000/μl; hemoglobin 9 g/100 ml; adequate renal and liver functions; no serious medical illness, psychiatric illness, or neurological problems; no known brain metastasis; and signed informed consent.

Caracemide was administered at a dose of 650 mg/m^2 daily $\times$ 5 days by continuous infusion through a central venous access catheter, repeated every 21 days until disease progression. Dose modifications were based on the degree of toxicity using the Cancer and Leukemia Group B criteria.

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Total entered	18
Total evaluable	15
Sex	
Male	11
Female	4
Median age in yrs (range): 61 (43-73)	
Histology	
Squamous cell carcinoma	7
Adenocarcinoma	5
Adenosquamous carcinoma	2
Large cell anaplastic carcinoma	1
Prior treatment	
Surgery	3
Radiation therapy	1
Surgery and radiation therapy	4
Site of extrathoracic lesions*	
Bone	2
Liver	3
Adrenal gland	2
Skin and sc tissue	4
Lymph nodes	3
Median Karnofsky performance status: 80%	
Total No. of courses: 32	
Median No. of courses/patient (range): 2 (1-4)	
Toxicity	
Nausea and vomiting	
Mild	2
Moderate	4
Severe	3
Diarrhea	2
Transient elevation of liver enzymes	1
Proteinuria	1
Anemia	
Mild	2
Requiring transfusion	4
Neurological toxic effects	
Drowsiness	1
Seizure activity	1

Continued

[1] Received June 15, 1987; revised July 21, 1987; accepted July 24, 1987.

[2] Supported in part by contract N01-CM-57734 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

[3] Division of Oncology, Department of Medicine, University of Maryland Hospital, University of Maryland Cancer Center, and Baltimore Veteran's Administration Medical Center.

* *Reprint requests to:* Chandra P. Belani, MD, Division of Oncology, Department of Medicine, University of Maryland Cancer Center, 22 S Greene St, Baltimore, MD 21201.

TABLE 1.—*Continued*

Characteristic	No. of patients
Response	
Complete + partial	0
Median time to disease progression in days: 40	
Median survival time in days (range): 96 (21-301+)	

*All patients had lung involvement.

RESULTS

Eighteen patients were considered eligible; 15 of these were fully evaluable for response (table 1). One patient was inevaluable because she received intrapleural caracemide, and there were two early deaths.

Overall, toxicity was mild. Nausea and vomiting were the most important side effects. Two patients developed diarrhea and one had transient elevation of liver enzymes. One patient developed proteinuria with reversible renal dysfunction. No myelosuppression was seen but two patients developed infection.

In summary, caracemide given at this dose and schedule has shown no evidence of antitumor activity in non-small cell lung carcinoma. Because of dose-limiting neurological toxicity observed in phase I trials, further increase of caracemide dose is not possible. This may in fact explain the lack of antitumor activity observed in this trial. No responses among 15 evaluable patients precludes a 20% level of activity with $> 95\%$ confidence.

REFERENCES

1. AISNER J, and HANSEN HH. Commentary: current status of chemotherapy for non-small cell lung cancer. Cancer Treat Rep 65:979-986, 1981.
2. BAKOWSKI MT, and CRONCH JC. Chemotherapy of non-small cell lung cancer: a reappraisal and a look to the future. Cancer Treat Rev 10:159-172, 1983.
3. Clinical Brochure. Caracemide (NSC-253272). Bethesda, MD, National Cancer Institute, Aug 1983.
4. RABER MN, ADAMS F, KAVANAGH J, ET AL. Phase I trial of caracemide using bolus and infusion schedules. Cancer Treat Rep 71: 349-352, 1987.

Phase II Trial of Bisantrene in Hepatocellular Carcinoma: A Southwest Oncology Group Study[1,2,3]

Thomas D. Brown,[4] Thomas R. Fleming,[5] Richard A. Shildt,[4] and John D. Cowan[4,6,*]

Bisantrene is one of a series of synthesized anthracenedicarboxaldehyde hydrazones with a wide spectrum of preclinical activity in animal systems (1). Bisantrene is thought to act as an intercalating agent with inhibition of ^{3}H-thymidine incorporation into DNA that is three times that of doxorubicin and is not cell cycle phase specific (1,2). In dogs, when bisantrene and doxorubicin were given in equally myelosuppressive doses, only doxorubicin demonstrated histological evidence for myocardial damage (3). Phase I evaluation of bisantrene given as a 30-minute infusion once every 3 weeks demonstrated a maximally tolerated dose of 280 mg/m^2, with the dose-limiting toxic effect being leukopenia (4).

MATERIALS AND METHODS

Patients with a pathologically verified diagnosis of advanced and measurable hepatoma were eligible for study entry. Patients were at least partially ambulatory [Southwest Oncology Group (SWOG) performance status ≤ 3]; with a wbc count > 4000/mm^3; platelet count $> 125{,}000$/mm^3; serum creatinine ≤ 2.0 mg/m^2; and serum bilirubin ≤ 2.0 mg/100 ml. Patients with cumulative doses of doxorubicin > 400 mg/m^2 or with a history of cardiac arrhythmias requiring therapy, congestive heart failure, or ischemic heart disease were not eligible. All patients gave written informed consent.

Bisantrene was administered in 500 ml of 5% dextrose in water over 2 hours if given peripherally and over 1 hour if given centrally, with repetition every 21 days. The starting dose was 260 mg/m^2 with a 10% dose escalation if toxicity was not observed and a 20% dose de-escalation for persistent grade 1 or 2 toxicity or for any reversible grade 3 toxicity. Responses were classified by the standard SWOG definitions (5).

RESULTS

Twenty-one patients from 14 SWOG institutions were entered in the study. Patient characteristics are shown in table 1. Seventeen patients received the drug by peripheral venous access and four by central venous access. All patients were eligible and fully evaluable for toxic effects, with 20 patients evaluable for response. There were no complete or partial responders. One patient died during his first course of drug due to treatment-related granulocytopenia with infection. The most common toxic effect was granulocytopenia, occurring in nine patients, with four of these patients experiencing SWOG grade ≥ 3 toxicity (< 500 granulocytes/mm^3). Four patients experienced thrombocytopenia, with one patient having SWOG grade ≥ 3 toxicity (platelet count $< 50{,}000$/mm^3). Other toxic effects of SWOG grade ≤ 2 included: anemia (five patients), nausea and vomiting (five patients), and phlebitis at the infusion site (one patient). One patient with a prior his-

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Sex	
Male	15
Female	6
Median age in yrs (range): 61 (19–81)	
Median (SWOG) performance status (range): 1 (1–3)	
Prior therapy (doxorubicin)	
None	14
Chemotherapy only	6 (6)
Radiotherapy only	0
Both	1 (1)

[1] Received Mar 17, 1987; revised July 16, 1987; accepted July 30, 1987.
[2] Supported in part by Public Health Service grants CA-22411, CA-37429, CA-04915, CA-03389, CA-37981, CA-12644, CA-20319, CA-28862, CA-13612, CA-32734, CA-12213, CA-13238, CA-22433, CA-14028, and CA-32102 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.
[3] The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the view of the Department of the Army or the Department of Defense.
[4] Brooke Army Medical Center, Fort Sam Houston, TX.
[5] Southwest Oncology Group Biostatistical Center, Seattle, WA.
[6] We thank Darlene DeWitt for assistance in preparation of the manuscript.

* *Reprint requests to:* Southwest Oncology Group (SWOG-8119), Operations Office, 5430 Fredericksburg Rd, Suite 618, San Antonio, TX 78229.

tory of supraventricular tachycardia developed a recurrence of such requiring antiarrhythmic therapy, and one patient developed asymptomatic hypotension during drug infusion with prompt response to fluid administration. The median survival of patients from time of registration in this study was 3 months (range, 1–14).

DISCUSSION

Bisantrene was well-tolerated with the exception of one treatment-related death due to drug-related granulocytopenia. In fact, a majority of patients experienced no myelosuppression. The lack of antitumor activity observed is disappointing, with a minority of patients having received prior antitumor therapy. The poor median survival of patients from time of registration suggests a population with advanced disease. Although more aggressive dose escalation to individual patient tolerance (ie, myelosuppression) might lead to some observed antitumor activity, this trial has demonstrated that bisantrene does not have significant antitumor activity against hepatocellular carcinoma.

REFERENCES

1. CITARELLA RV, WALLACE RE, MURDOCK KC, ET AL. Antitumor activity of CL 216,942 9,10-anthracenedicarboxaldehyde bis ([4,5 dihydro-1*H*-imidazol-2-yl] hydrazone) dihydrochloride. *In* Proceedings of the 20th Interscience Conference on Antimicrobial Agents and Chemotherapy, Sept 1980, Abstr 23.
2. WALLACE RE, CITARELLA RV, and DURR FC. The inhibitory effects of CL 216,942 9,10-anthracenedicarboxaldehyde bis ([4,5 dihydro-1*H*-imidazol-2-yl] hydrazone) dihydrochloride. *In* Proceedings of the 20th Interscience Conference on Antimicrobial Agents and Chemotherapy, Sept 1980, Abstr 28.
3. SPARANO BM, GORDON G, HALL C, ET AL. Assessment of cardiotoxic potential of a new anticancer compound, an anthracene-bishydrazone derivative in beagle dogs: comparison with Adriamycin. *In* Proceedings of the 20th Interscience Conference on Antimicrobial Agents and Chemotherapy, Sept 1980, Abstr 31.
4. VON HOFF DD, MYERS JW, KUHN J, ET AL. Phase I clinical investigation of 9,10-anthracenedicarboxaldehyde bis ([4,5 dihydro-1*H*-imidazol-2-yl] hydrazone) dihydrochloride (CL 216,942). Cancer Res 41:3118, 1981.
5. MILLER AB, HOOGSTRATEN B, STAQUET M, ET AL. Reporting results of cancer treatment. Cancer 47:207–214, 1981.

Phase II Trial of Ifosfamide/Mesna in Metastatic Adult Renal Carcinoma[1]

A. De Forges, J. P. Droz,* M. Ghosn, and C. Theodore[2,3]

Ifosfamide is an alkylating oxazaphosphorine with proven activity in a wide variety of tumors (1). Between June 1, 1985, and July 31, 1986, 19 adult patients with measurable metastatic renal cell carcinoma were entered in a phase II trial of ifosfamide. Patient characteristics are listed in table 1.

Ifosfamide was given at a dosage of 3 g/m^2 daily in 1 L of 5% dextrose in water in a 3-hour perfusion for 2 consecutive days every 4 weeks. Mesna was simultaneously administered at 3.6 g/m^2 per day; 600 mg/m^2 was given as an iv bolus 30 minutes before ifosfamide perfusion, and 1200 mg/m^2 was given simultaneously with the ifosfamide perfusion, followed by continuous perfusion of 1800 mg/m^2 for 15 hours. The tumor response was assessed according to the World Health Organization response criteria 3 weeks after the administration of at least two cycles of therapy (2).

Three patients were not evaluable for response; two died following one course of chemotherapy, one patient from disease progression and the other from an undetermined cause. The third patient did not have well-defined measurable disease. In the 16 remaining patients, only one partial response (6%) of short duration (3 mos) was observed (95% confidence limits, 0%–18%). No life-threatening toxic effects were noted during the treatment. Nausea, vomiting, and alopecia were universal. No macroscopic hematuria, central nervous system toxicity, severe neutropenia, or hemorrhagic or infectious accidents were noted. One patient who had had nephrectomy developed a transient twofold rise in the serum creatinine level after two cycles of treatment.

Our results are in accordance with those of Fossâ and Talle (3), who observed one partial response in 11 patients treated with ifosfamide at a dosage of 50–60 mg/kg per day for 5 consecutive days, with or without irradiation. The use of continuous infusion of mesna seems to consistently prevent the development of gross aseptic hemorrhagic cystitis. We conclude that ifosfamide at this dose and with this schedule is not active in metastatic adult renal cell carcinoma.

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Total	19
Evaluable	16
Sex	
Male	12
Female	7
Median age in yrs (range): 57 (36–73)	
Performance status	
0–1	8
2–3	11
Initial nephrectomy	15
Sites of metastatic disease	
Lung	14
Lymph nodes	6
Bone	5
Liver	3
Other	5
Prior therapy for metastasis	
None	7
Chemotherapy	5
Surgery	4
Hormonal therapy	1
Radiation	1
Toxic effects	
Nausea and vomiting	19
Alopecia	17
Renal toxicity	1
Aplasia	0
Hemorrhagic cystitis	0
CNS toxicity	0

REFERENCES

1. BRADE WP, HERDRICH K, and VARINI M. Ifosfamide: pharmacology, safety and therapeutic potential. Cancer Treat Rev 12:1–47, 1985.
2. MILLER AB, HOOGSTRATEN B, STAQUET M, ET AL. Reporting results of cancer treatment. Cancer 47:207–214, 1981.
3. FOSSÅ SD, and TALLE K. Treatment of metastatic renal cell carcinoma with ifosfamide and mesnum with and without irradiation. Cancer Treat Rep 64:1103–1108, 1980.

[1] Received Apr 16, 1987; revised July 10, 1987; accepted July 30, 1987.
[2] Department of Medicine, Institut Gustave-Roussy, Villejuif, France.
[3] We thank Dr. V. Jebara for reviewing the manuscript and Mrs. M. Belleteste for her secretarial help.
* *Reprint requests to:* J. P. Droz, MD, Department of Medicine, Institut Gustave-Roussy, Rue Camille Desmoulins, 94800 Villejuif, France.

Phase II Study of Spirohydantoin Mustard for the Treatment of Recurrent Malignant Gliomas[1,2]

Michael Prados, Luis Rodriguez, Margaret Seager, Pamela Silver, and Victor Levin[3,*]

Spirohydantoin mustard (spiromustine) is a nitrogen mustard alkylating agent coupled with a pro-drug phenytoin carrier (1). It crosses the blood-brain barrier (2) and has shown activity against intracerebral tumors in animal models (3). It has also shown in vitro capabilities of blocking DNA synthesis (4). During a recent phase I study, it showed evidence of disease stabilization in some patients with primary and metastatic brain tumors (5). With this background, a phase II study was conducted using spiromustine for recurrent brain gliomas.

PATIENTS AND METHODS

Sixteen patients with radiographic and histologic documentation of a recurrent primary brain glioma were entered in the study. One patient was not evaluable for response due to severe neurotoxicity after the first dose preventing adequate further treatment. Patient characteristics are summarized in table 1.

Spiromustine was given as a rapid iv infusion at a dose of 3 mg/m^2 twice a week, with 2-4-day intervals between doses, for 3 consecutive weeks. The patients were evaluated 2 weeks after the sixth dose; if stable or improved contrast-enhanced computerized tomographic (CT) scans were seen, patients were re-treated at the same dose twice per week for 12 more doses with 2-week intervals between the sixth and seventh dose. Patients were then re-evaluated for response. At each evaluation period, patients had a clinical examination and contrast-enhanced CT scan.

Neurotoxicity was controlled with physostigmine at 1 mg im or iv given every hour as needed.

RESULTS

Eleven patients had immediate disease progression at the first evaluation. Four patients had stable disease at the first evaluation. Three of these four patients showed

TABLE 1.—Patient characteristics and treatment results

Characteristic	No. of patients
Entered/evaluable	16/15
Male/female	11/5
Median age in yrs (range): 43 (19-59)	
Histology	
Glioblastoma multiforme	11
Anaplastic astrocytoma	5
Karnofsky performance score (range, 60-100)	
Previous treatment	
Surgery	16
Radiotherapy	16
Chemotherapy (all received nitrosoureas)	15
Response	
Immediate progression	11
Stable disease (< 14 wks)	4
Stable disease (> 14 wks)	1
Toxicity*	
Restlessness/agitation	
Mild	1
Moderate	8
Confusion/hallucinations	
Mild	6
Moderate	8
Severe	3
Lethargy	
Mild	3
Moderate	3
Severe	1
Ataxia	
Mild	2
Moderate	2
Dysphasia	
Mild	1
Moderate	3
Deterioration of pre-existing motor or sensory deficit	
Mild	1
Moderate	3

*Mild (transient event); moderate (lasting > 30 min); and severe (requiring hospitalization).

[1] Received June 22, 1987; revised July 22, 1987; accepted July 30, 1987.

[2] Supported in part by Public Health Service grant CA-13525 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. M. Prados and L. Rodriguez are American Cancer Society Regular Clinical Fellows.

[3] Brain Tumor Research Center, Department of Neurological Surgery, University of California, San Francisco.

*_Reprint requests to:_ Victor A. Levin, MD, Brain Tumor Research Center, Department of Neurological Surgery, HSW 783, University of California, San Francisco, CA 94143-0520.

progression of their tumors at the second evaluation 14 weeks after initiation of treatment. There were no responses. One patient remained stable after the second evaluation but he was a passenger in a motor vehicle accident which rendered him permanently comatose.

Toxic reactions were confined only to the nervous system and they were all transitory. All patients exhibited neurotoxicity. Toxic effects are shown in table 1.

DISCUSSION

In this group of 16 patients with recurrent primary gliomas who had previously been treated with nitrosoureas, spiromustine had some evidence of activity (27%, stable disease), but only for a short duration. At a dose of 3 mg/m^2 twice a week, all patients developed neurotoxicity. Although we did not escalate dose, our clinical impression is that higher doses would be difficult to tolerate.

The role of spiromustine as a single agent in nitrosourea failures appears to be limited, but it may warrant investigation in combination with other drugs for the treatment of malignant gliomas.

REFERENCES

1. RODGERS TR, LA MONTAGNE MP, MARKOVIC A, ET AL. Hydantoins as antitumor agents. J Med Chem 20:591-594, 1977.
2. PLOWMAN J, LAKINGS DB, OWENS ES, ET AL. Initial studies on the penetration of spirohydantoin mustard. Pharmacology 15:359-366, 1977.
3. PENG GW, MARQUEZ VE, and DRISCOLL JS. Potential central nervous system antitumor agents: hydantoin derivatives. J Med Chem 18:846-849, 1975.
4. DEEN DF, HOSHINO T, WILLIAMS ME, ET AL. Response of 9L tumor cells in vitro to spirohydantoin mustard. Cancer Res 39: 4336-4340, 1979.
5. CURT GA, KELLEY JA, KUFTA CU, ET AL. A phase I and pharmacokinetic study of spiromustine in CNS malignancy. Proc ASCO 4:33, 1985.

Phase II Trial of Prednimustine as First-Line Chemotherapy in Patients With Advanced Breast Cancer[1]

E. M. Rankin,[2,*] C. Harvey,[3] R. K. Knight,[2] and R. D. Rubens[2]

Prednimustine, an ester of chlorambucil and prednisolone, is reported to have a response rate of up to 40% (1) in breast cancer. We have given prednimustine, 40 mg/m^2, continuously as first-line chemotherapy to women with advanced breast cancer.

PATIENTS AND METHODS

Details of the patients in the study are shown in table 1. Prednimustine, 40 mg/m^2 daily, in two divided doses was given continuously until progression of disease unless toxicity occurred. The blood count was checked weekly for the first month and at least monthly thereafter. The dose was modified as follows: for a wbc count of 2–4 $\times$ 10^9/L or a platelet count of 70–120 $\times$ 10^9/L, a 50% dose was given; for a wbc count $< 2 \times 10^9$/L or a platelet count of $< 70 \times 10^9$/L, treatment was discontinued until the blood count rose sufficiently to allow a 50% dose. Objective response was assessed using International Union Against Cancer criteria (2).

RESULTS

A total of 23 patients entered the study; all were assessable for toxic effects and 22 were evaluable for response. One patient with leukopenia developed septicemia and died before response could be assessed. Eleven patients received prednimustine for > 2 months, eight stopped early because of progressive disease, and treatment was discontinued in four because of toxic effects. Two patients achieved a partial response; the sites involved were liver and lymph nodes in one case and skin in the other.

Three patients had had no prior systemic therapy; the rest had received hormonal therapy only for advanced disease. Thirteen patients had received prednisolone or hydrocortisone as part of their treatment immediately before entry to this trial. There was no correlation between response and prior steroid therapy.

TABLE 1.—Patient characteristics, response, and toxic effects

	No. of patients
Median age at entry in yrs (range): 60 (30–84)	
Median age at diagnosis in yrs (range): 55 (30–77)	
Median disease-free interval in mos (range): 31 (1–84)	
Stage at diagnosis	
I and II	9
III and IV	13
Not known	1
Histological grade of tumor	
I	1
II	3
III	8
Not known	11
Receptor status	
ER positive	1
ER negative	9
ER not known	6
Performance status at entry	
0	6
1	12
2	5
Previous treatment	
Surgery for primary operable disease	15
Radiotherapy for primary inoperable disease	7
Adjuvant chemotherapy*	4
No. of endocrine treatments	
0	3
1	6
2	9
3	5
Response	
Partial response (durations: 18 and 21 wks)	2
No change	6
Progressive disease	14
Not evaluable	1

Continued

[1] Received Feb 20, 1987; revised July 30, 1987; accepted Aug 3, 1987.

[2] Imperial Cancer Research Fund, Clinical Oncology Unit, Guy's Hospital, London, England.

[3] Smith, Kline and French Research Ltd, The Frythe, Welwyn, Hertfordshire, England.

**Reprint requests to:* Elaine M. Rankin, MD, Department of Medical Oncology, University of Glasgow, 1 Horselethill Rd, Glasgow G12 9LX, Scotland.

TABLE 1.—*Continued*

	No. of patients
Toxicity†	
Hemoglobin	
Grade III	2
Grade IV	0
Wbc count	
Grade III	3
Grade IV	3
Platelet count	
Grade III	1
Grade IV	0

*Median interval since adjuvant chemotherapy in mos (range): 69 (37–88).

†World Health Organization criteria (ref 3).

Hematological toxicity was severe and unpredictable, with nine patients developing severe (grade III or IV) (3) hematological toxicity. Grade IV leukopenia was seen in three patients, two of whom developed septicemia leading to death in one and contributing to death in the other. A prolonged depressive effect on the bone marrow was seen after the discontinuation of prednimustine.

DISCUSSION

The disappointing response rate (9%) and severe toxicity in the study mean that continuous prednimustine at 40 mg/m^2/day cannot be recommended for advanced breast cancer.

REFERENCES

1. LOBER J, MOURIDSEN HT, CHRISTIANSEN IE, ET AL. A phase III trial comparing prednimustine (LEO 1031) with chlorambucil plus prednimustine in advanced breast cancer. Cancer 52:1570–1576, 1983.
2. HAYWARD JL, CARBONE PP, HEUSON J-C, ET AL. Assessment of response to therapy in advanced breast cancer. Eur J Cancer 13:89–94, 1977.
3. WORLD HEALTH ORGANIZATION. Handbook for Reporting Results of Cancer Treatment. WHO Offset Publ No. 48, Geneva, WHO, 1979.

Phase II Study of Mitoxantrone in Untreated and Previously Minimally Treated Patients With Metastatic Soft Tissue Sarcomas[1,2]

Ian Quirt,* Elizabeth Eisenhauer, Vivien Bramwell, Margaret Knowling, Clive Grafton, Wolfgang Hirte, Mary Cripps, and Andrew Maksymiuk[2]

Mitoxantrone has been studied in patients with soft tissue sarcoma (1,2). The results were disappointing, but most patients had had prior doxorubicin therapy and the doses of mitoxantrone given were not high. This study examined an escalating dose of mitoxantrone in patients who had never received doxorubicin or who had received adjuvant doxorubicin in the distant past.

MATERIALS AND METHODS

Eligible patients had histologically proven measurable soft tissue sarcoma as defined by the American Joint Committee for Cancer Staging and End Result Reporting (3) and were either previously untreated or had completed adjuvant chemotherapy > 6 months before mitoxantrone treatment. They were ≥ 16 years of age and their left ventricular ejection fraction (LVEF) was > 50%. Laboratory requirements were a platelet count > 125,000/mm^3, absolute granulocyte count > 2000/mm^3, bilirubin < 1.5 g/dl, and creatinine < 1.5 g/dl.

The starting dose of mitoxantrone was 14 mg/m^2 as a single iv injection every 3 weeks. Blood cell counts were obtained weekly. If the nadir absolute granulocyte count was < 500/mm^3 or the nadir platelet count was < 50,000/mm^3, the dose was reduced to 12 mg/m^2 for the second course. If the nadir absolute granulocyte count was > 750/mm^3 and the nadir platelet count was > 100,000/mm^3, the dose was increased by 2 mg/m^2 for each subsequent course. Patients were reassessed every 3 weeks.

RESULTS AND DISCUSSION

A total of 27 patients were entered. Two were ineligible, one because of a low wbc count and the other because of an LVEF of 40%. The patient characteristics, response, and toxic effect are summarized in tables 1 and 2. Fifty-four cycles of chemotherapy were given. In seven patients the dose was escalated and in four patients myelosuppression necessitated dose reduction.

TABLE 1.—Patient characteristics and response

Characteristic	No. of patients
Sex	
Male	16
Female	9
Performance status*	
0	5
1	14
2	4
3	0
4	2
Previous chemotherapy	
None	22
Adjuvant	3†
Pathology	
Leiomyosarcoma	6
Malignant fibrous histiocytoma	5
Liposarcoma	2
Fibrosarcoma	1
Other	11
Response	
Complete	0
Partial	2‡
Stable disease	4
Disease progression	19

*Eastern Cooperative Oncology Group criteria.
†All doxorubicin-containing.
‡Durations 4 mos and 6 mos.

[1] Received Apr 16, 1987; revised July 14, 1987; accepted Aug 3, 1987.
[2] This study was conducted by the National Cancer Institute of Canada Clinical Trials Group and was supported by grants from the National Cancer Institute of Canada and Lederle International Clinical Research. The following members participated in the study: Princess Margaret Hospital, Toronto, Ontario (*I. Quirt, J. Meharchand,* and *D. Warr*); The Ontario Cancer Foundation, Ottawa Regional Centre (*M. Cripps, W. Hirte, D. Perrault, J. Maroun,* and *D. Stewart*); The Ontario Cancer Foundation, London Regional Centre, London (*V. Bramwell*); The Cancer Control Agency of British Columbia, Vancouver (*M. Knowling* and *C. Grafton*); University Hospital, Saskatoon, Saskatchewan (*A. Maksymiuk*); W. W. Cross Cancer Institute, Edmonton, Alberta (*P. Venner*); The Ontario Cancer Foundation, Toronto Bayview Regional Centre (*J. Rusthoven*); and the National Cancer Institute of Canada Investigational New Drug Program Office, Kingston, Ontario (*E. Eisenhauer*).
**Reprint requests to:* Dr. Ian Quirt, Princess Margaret Hospital, 500 Sherbourne St, Toronto, Ontario, Canada M4X 1K9.

TABLE 2.—Toxic effect: myelosuppression

Dose level (mg/m^2)	No. of cycles evaluable	Median nadir neutrophil count/mm^3 (range)	Median nadir platelet count/mm^3 (range)
12	7	350 (100–1300)	208,000 (143,000–345,000)
14	42	800 (80–2500)	251,000 (88,000–672,000)
16	5	450 (40–700)	209,000 (60,000–273,000)

Toxicity was primarily myelosuppression. No cases of life-threatening infection or bleeding were observed. Three patients developed mild hair loss, four developed mild nausea and vomiting, and two developed moderate nausea and vomiting. No cardiac complications were documented.

We observed two partial responses lasting 4 and 8 months. The vast majority of patients had received no prior chemotherapy. No patient responded to dose escalation.

We conclude that mitoxantrone will not contribute significantly to the first-line therapy of soft tissue sarcoma.

REFERENCES

1. GAMS RA, OSTROY F, BARTOLUCCI AA, ET AL. Phase II studies of mitoxantrone in the Southeastern Cancer Study Group. *In* New Anticancer Drugs: Mitoxantrone and Bisantrene (Rozencweig M, et al, eds). New York, Raven Press, 1983.
2. BULL FE, VON HOFF DD, BALCERZAK SP, ET AL. Phase II trial of mitoxantrone in advanced sarcomas: a Southwest Oncology Group study. Cancer Treat Rep 69:231–233, 1985.
3. RUSSELL WO, COHEN J, ENZINGER F, ET AL. A clinical and pathological staging system for soft tissue sarcoma. Cancer 40:1562–1570, 1977.

Phase II Study of Fludarabine Phosphate in Previously Untreated Patients With Hepatoma: A Southwest Oncology Group Study[1,2,3]

Walter H. Harvey,[4] Thomas R. Fleming,[5] German Beltran,[6] J. H. Saiers,[7] Norboru Oishi,[8] and Daniel D. Von Hoff[9,10,*]

Fludarabine phosphate (2-FLAMP) is an analog of vidarabine which has shown preclinical antitumor activity (1). 2-FLAMP was evaluated in a phase II study of previously untreated patients with hepatoma.

All patients had a diagnosis of hepatoma, had not received any chemotherapy, and had measurable disease. Hematologic and renal function parameters were normal at the start of therapy. No patients received other therapy while on the protocol and all patients gave written informed consent according to institutional review board and Food and Drug Administration guidelines.

All patients were registered through the Southwest Oncology Group statistical office. 2-FLAMP was administered iv as a rapid bolus infusion at a dose of 25 mg/m^2/day × 5 repeated every 28 days. Dose escalation to 31.25 mg/m^2/day was permitted, and dose decrease to 18.75 mg/m^2/day was done for unacceptable toxicity. Standard response and toxicity criteria, according to Southwest Oncology Group guidelines, were used.

Nineteen patients were entered in the study. Two patients were ineligible due to elevated bilirubin (13 and 5.3 mg/100 ml) on the initial day of treatment. Seventeen patients were eligible for the study, with 16 being fully evaluable for response and toxic effects. One patient died before receiving therapy. Patient characteristics, response, and toxic effects are shown in table 1.

A total of 37 courses of therapy were given. No responses to 2-FLAMP in this dose or schedule were noted. Toxic effects of 2-FLAMP were primarily myelosuppressive and neurologic. Eight patients developed

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Entered	19
Eligible (males/females)	17 (10/7)
Evaluable for response and toxicity	16
Median age in yrs (range): 63 (36–72)	
Courses evaluable	
18.75 mg/m^2/day × 5: 3	
25 mg/m^2/day × 5: 28	
31.25 mg/m^2/day × 5: 6	
Responses	
Complete	0 (0%)
Partial	0 (0%)
None/stable disease	3 (18%)
Disease progression	13 (76%)
Early death	1 (6%)
Toxic effects	
Granulocytopenia (cells/mm^3)	
< 1500	1
< 1000	2
< 500	4
< 250	1
Thrombocytopenia (cells/mm^3)	
75,000–99,999	3
50,000–74,999	1
25,000–49,999	0
< 25,000	2
Somnolence/neuromuscular	7/2
Nausea and vomiting	4
Diarrhea	3
Anemia	2
Rash	1

[1] Received May 19, 1987; revised July 27, 1987; accepted Aug 3, 1987.
[2] Supported in part by grants CA-22411, CA-37429, CA-03389, CA-12213, CA-32734, CA-04919, CA-35176, CA-35438, CA-04920, CA-20319, CA-37981, CA-03096, CA-32102, and CA-22433 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.
[3] The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the view of the Department of the Army or the Department of Defense.
[4] Brooke Army Medical Center, Fort Sam Houston, TX.
[5] Southwest Oncology Group Biostatistical Center, Seattle, WA.
[6] Tulane University Medical Center, New Orleans, LA.
[7] Albuquerque VA Medical Center, NM.
[8] Cancer Center of Hawaii, Honolulu.
[9] University of Texas Health Science Center, San Antonio.
[10] We thank Darlene DeWitt for assistance in preparation of the manuscript.

* *Reprint requests to:* Southwest Oncology Group (SWOG-8318), Operations Office, 5430 Fredericksburg Rd, Suite 618, San Antonio, TX 78229.

granulocytopenia, with seven having absolute nadir granulocyte counts < 1000/mm^3. Six patients had platelet counts < 100,000/mm^3, with two manifesting platelet counts < 25,000/mm^3. Seven patients had somnolence during the 2-FLAMP infusion. The somnolence cleared in all patients within hours after the infusion was complete. Two patients had peripheral muscle weakness. One patient, with previously diagnosed diabetes mellitus, noted lower-extremity weakness and burning paresthesias on Day 15 after the first course of therapy. This resolved within 24 hours. The patient was taken off study and received no further 2-FLAMP. The second patient had weakness for 1 week after receiving 2-FLAMP. The weakness was resolved prior to the next course and no further episodes of weakness occurred after two further courses at the reduced dose level. Other side effects were infrequent and minimal and are shown in table 1.

Since no antitumor responses were seen in this study, further use of 2-FLAMP in the treatment of hepatoma is not warranted using this dose and schedule. This study confirms that primary myelotoxicity and neurotoxicity are associated with 2-FLAMP administration as previously reported, although neurotoxicity was mild and self-limited in this study (2–4). Further studies using 2-FLAMP should address in a specific fashion the subclinical and clinical neurotoxicity associated with this agent.

REFERENCES

1. BROCKMAN RW, CHENG Y-C, SCHABEL FM, JR, ET AL. Metabolism and chemotherapeutic activity of 9-beta-D-arabinofuranosyladenine against murine leukemia L1210 and evidence for its phosphorylation by deoxycytidine kinase. Cancer Res 40:3610–3615, 1980.
2. HUTTON JJ, VON HOFF DD, KUHN J, ET AL. Phase I clinical investigation of 9-beta-D-arabinofuranosyl-2-fluoroadenine 5'-monophosphate (NSC-312887), a new purine antimetabolite. Cancer Res 44: 4183–4186, 1984.
3. LEIBY JM, GREVER MR, STAUBUS AE, ET AL. A phase I clinical investigation of fludarabine phosphate by loading dose/continuous infusion. Proc Am Assoc Cancer Res 26:169, 1985.
4. WARRELL RP, and BERMAN E. Phase I and II study of fludarabine phosphate in leukemia: therapeutic efficacy with delayed central nervous system toxicity. J Clin Oncol 4:74–79, 1986.

Continuous-Infusion Amsacrine in Patients With Refractory Acute Myelogenous Leukemia[1]

Elihu H. Estey,* Michael J. Keating, Kenneth B. McCredie, and Emil J Freireich[2]

Because amsacrine-induced DNA cleavage disappears rapidly following removal of cultured acute myelogenous leukemia (AML) cells into drug-free medium (1) and because free amsacrine has a short serum half-life (2), we administered amsacrine by continuous infusion rather than bolus injection to patients with AML. We chose a starting dose of 90 mg/m^2/day for 5 days. Lower doses given by bolus injection had produced lower complete response (CR) rates in AML (3). Phase I trials in patients with solid tumors had shown that the maximum tolerated dose (30 mg/m^2/day × 3) and the dose-limiting toxicity (myelosuppression) were identical with continuous-infusion and bolus injection schedules (4).

PATIENTS AND METHODS

Twenty-one adults were entered in the study (table 1). Criteria for entry were (*a*) > 30% myeloblasts in the bone marrow; (*b*) failure to enter initial CR or relapse following achievement of CR; (*c*) Zubrod performance status of 0, 1, or 2; (*d*) normal serum bilirubin; and (*e*) written informed consent.

RESULTS

No CRs occurred. The 95% confidence limits were 16%–23%, considering only the patients who were not previously exposed to amsacrine. There were two early deaths. Bone marrow aplasia occurred in 14 patients; nine of these died in aplasia (four during the first course), and five had recurrence of AML. Aplasia persisted for 35 days after drug administration in one patient.

Hyperbilirubinemia occurred in 16 patients and was not dose-related. Gram-negative sepsis and/or *Candida* sepsis occurred in 14 patients, and all of them developed hyperbilirubinemia. Mucositis occurred in 13 patients; ten developed gram-negative sepsis and/or *Candida* sepsis. Ten of the 11 deaths in the study were due to infection.

DISCUSSION

The 0% CR rate contrasts with higher CR rates following bolus injection of amsacrine in patients with refractory AML: 27% (95% confidence limits, 18%–38%) at M. D. Anderson Hospital and a similar percent in other studies (3,5). Aplasia apparently occurs with equal frequency in the two schedules, but death during the study and hyperbilirubinemia appear to occur more frequently with the continuous-infusion schedule (3,5). Although amsacrine may directly produce hyperbilirubinemia (3), the association among hyperbilirubinemia, sepsis, and mucositis suggests that the use of amsacrine by continuous infusion increases cytotoxicity to the gastrointestinal tract, predisposing the patient to enteric organism sepsis with resultant hyperbilirubinemia and death.

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Entered	21
Evaluable	21
Failed initial induction therapy	6
Relapsed	15*
Prior salvage regimens	
0	4
1	9
≥2	8
Prior amsacrine/cytarabine as initial induction therapy	7
1st course dose (mg/m^2/day × 5)	
90	10
120	3
150	7
200	1

* Median initial duration of CR = 6 mos.

[1] Received Mar 26, 1987; revised July 21, 1987; accepted Aug 13, 1987.
[2] Department of Hematology, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston.

* *Reprint requests to:* Elihu H. Estey, MD, Department of Hematology, Box 47, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, 1515 Holcombe Blvd, Houston, TX 77030.

REFERENCES

1. ZWELLING LA, MICHAELS S, ERICKSON LC, ET AL. Protein-associated deoxyribonucleic acid strand breaks in L1210 cells treated with the deoxyribonucleic acid intercalating agents 4'-(9-acridinylamino)methanesulfon-*m*-anisidide and Adriamycin. Biochemistry 20:6553–6563, 1981.
2. VAN ECHO DA, CHIUTEN DF, GORMLEY PE, ET AL. Phase I clinical and pharmacological study of 4'-(9-acridinylamino)methanesulfon-*m*-anisidide using an intermittent biweekly schedule. Cancer Res 39:3881–3884, 1979.
3. LEGHA SS, KEATING MJ, MCCREDIE KB, ET AL. Evaluation of AMSA in previously treated patients with acute leukemia: results of therapy in 109 adults. Blood 60:484–490, 1982.
4. MICETICH KC, ZWELLING LA, GORMLEY P, ET AL. Phase I–II study of *m*-AMSA administered as a continuous infusion. Cancer Treat Rep 66:1813–1817, 1982.
5. WINTON EF, HEARN EB, VOGLER WR, ET AL. Amsacrine in refractory adult acute leukemia: a pilot study of the Southeastern Cancer Study Group. Cancer Treat Rep 67:977–980, 1983.

Ifosfamide Plus 5-Fluorouracil for Treatment of Adenocarcinoma of the Pancreas[1,2]

Patrick J. Loehrer, Sr,* Stephen D. Williams, and Craig R. Nichols[3]

Activity of ifosfamide (IFX) for the treatment of patients with pancreatic cancer has been reported by several investigators (1,2). In 1985, we reported response in six of 29 patients treated with the single agent IFX administered at dosages of 1.25–2.0 g/m^2 daily for 5 days every 3 weeks (2). Based on this activity and apparent synergism of these compounds (3), we chose to evaluate IFX plus 5-FU in the treatment of patients with advanced pancreatic cancer.

PATIENTS AND METHODS

From July 1984 to January 1986, 30 patients with biopsy-proven, advanced adenocarcinoma of the pancreas were entered in the study. Patient characteristics are shown in table 1. All patients had a KPS $\geq$ 50, bidimensionally measurable disease, and no prior chemotherapy or radiotherapy within 3 weeks of entering the study. All patients had serum creatinine and bilirubin levels $\leq$ 2.0 mg/dl and adequate bone marrow reserve.

The IFX (1.5 g/m^2) and 5-FU (300 mg/m^2) were administered daily for 5 consecutive days every 3 weeks. Mesna (400 mg/m^2) was administered immediately prior to IFX and every 4 hours for three total doses on Days 1–5 for uroprotection, with continuous hydration using 0.45 N saline. Standard criteria for response were used.

RESULTS

Of the 30 patients entered in the study, one was never treated and 29 were fully evaluable; two (7%) had partial response (95% confidence limits, 0.85%–22.7%); ten (34%) had stable disease; and 17 (59%) had progressive disease. The durations of partial remissions were 4 and 52 weeks. The median survival time of all eligible patients was 18 weeks (range, 2–112).

Toxic effects are shown in table 1. The wbc count nadir was 1900/mm^3, and the absolute granulocyte count nadir was < 1000/mm^3.

TABLE 1.—Patient characteristics*

Characteristic	No. of patients
Entered	30
Refused treatment	1
Evaluable	29
Sex	
Male	15
Female	15
Median age in yrs (range): 64 (40–76)	
Metastatic sites	
Locally advanced only	9
Liver	12
Lung	3
Lymph node	2
Median KPS (range): 80 (50–100)	
Prior surgery	
None	13
Cholecystojejunostomy	5
Gastrojejunostomy	3
Other	8
Response	
Partial	2 (7%)
Stable disease	10 (34%)
Disease progression	17 (59%)
Toxic effects	
Nausea/vomiting (moderate/severe)	11 (35%)
Granulocytopenic fever	5 (17%)
Sepsis	1 (3%)
CNS (confusion/lethargy)	6 (20%)
Urticaria	1 (3%)

*KPS = Karnofsky performance status.

DISCUSSION

This study fails to confirm substantial activity for IFX plus 5-FU in the treatment of pancreatic cancer. Recently, the Mid-Atlantic Oncology Program reported only one partial remission in 29 evaluable patients treated with IFX (4). Although iv mesna was used

[1] Received Mar 16, 1987; revised July 21, 1987; accepted Aug 17, 1987.
[2] Supported in part by Bristol-Myers Co and in part by Public Health Service grant RR-00750 from the Division of Research Resources, National Institutes of Health, Department of Health and Human Services.
[3] Department of Medicine, Indiana University Medical Center, Indianapolis.
* *Reprint requests to:* Patrick J. Loehrer, Sr, MD, Department of Medicine, Indiana University Medical Center, Rm A-109, W Michigan St, Indianapolis, IN 46223.

instead of oral *N*-acetylcysteine (used in our previous study), preclinical data do not suggest that mesna antagonizes the cytotoxic effects of oxazaphosphorines (5). As the response rate and survival in this series are comparable to those previously observed for single-agent 5-FU, further studies with IFX at this dosage and schedule in this disease do not appear to be warranted.

REFERENCES

1. GAD-EL-MAWLA N. Ifosfamide treatment of pancreatic cancer. Cancer Treat Rep 65:357-358, 1981.
2. LOEHRER PJ, SR, WILLIAMS SD, EINHORN LH, ET AL. Ifosfamide: an active drug in the treatment of adenocarcinoma of the pancreas. J Clin Oncol 3:367-372, 1985.
3. GOLDIN A. Ifosfamide in experimental tumor systems. Semin Oncol 9(suppl 1):14-23, 1982.
4. BERNARD S, NOBLE S, WILCOSKY T, ET AL. A phase II study of ifosfamide plus *N*-acetylcysteine in metastatic measurable pancreatic adenocarcinoma. Proc ASCO 5:84, 1986.
5. BROCK N, POHL J, and STEKAR J. Studies on the urotoxicity of oxazaphosphorine cytostatics and its prevention. I. Experimental studies on the urotoxicity of alkylating compounds. Eur J Cancer 17: 595-607, 1981.

Phase II Study of Deoxydoxorubicin in Patients With Advanced Liver Cancer[1,2]

David J. Perry,* David A. Van Echo, and Rosemarie Mick[2]

For the Cancer and Leukemia Group B

Deoxydoxorubicin is a doxorubicin analog in which the 4′-hydroxyl group of the amino sugar has been removed (1). The drug demonstrated antitumor activity similar to that of doxorubicin in testing against a spectrum of murine tumors and human xenografts but showed significantly less cardiotoxicity in mice, dogs, and rabbits. We report a phase II trial of deoxydoxorubicin in hepatocellular carcinoma.

PATIENTS AND METHODS

Patients with measurable and histologically confirmed unresectable or metastatic primary liver cancer (hepatocellular carcinoma) were eligible for the study. A Cancer and Leukemia Group B performance status of 2 or better was required. Patients were ineligible if < 1 week had elapsed since major surgery or < 4 weeks since palliative radiotherapy or if they had received prior chemotherapy, had severe cardiovascular disease, or had a history of prior malignancies. Required pretreatment laboratory values were wbc count $> 3500/\mu l$; platelet count $> 100{,}000/\mu l$; hemoglobin > 10 g/dl; and BUN, creatinine, and bilirubin < 1.5 times normal. Deoxydoxorubicin (30 mg/m^2) was diluted in normal saline and administered iv over at least 10 minutes once every 3 weeks. At least two courses were administered in the absence of objective disease progression or severe toxicity. Dose modifications were specified for hematologic and hepatic toxic effects. Survival estimates were calculated utilizing standard Kaplan-Meier life tables (2).

Between December 1984 and September 1986, 41 patients were entered in the trial; two were canceled prior to receiving treatment. Three patients were ineligible: one patient had an elevated pretreatment bilirubin, one

TABLE 1.—Patient characteristics

	No. of patients	%
Age (yrs)		
< 60	19	54
≥ 60	16	46
Sex		
Male	24	69
Female	11	31
Prior treatment		
Surgery	26	74
Radiotherapy	2	6
Performance status		
0-1	26	74
2	9	26
Initial bilirubin (mg/dl)		
0-1.0	20	59
≥ 1.1	14	41
Sites of metastatic disease		
Lung	2	6
Bone	2	6
Distant lymph nodes	1	3
Skin	1	3
Pleura	1	3
Other*	4	11

*Ascites (1 patient), alpha-fetoprotein (2), and paraspinal mass (1).

[1] Received May 20, 1987; revised July 20, 1987; accepted Aug 17, 1987.

[2] This study was conducted by the Cancer and Leukemia Group B and was supported by Public Health Service grants (CA) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and by a grant from the T. J. Martell Foundation for Leukemia and Cancer Research. The following members participated in this study: University of California at San Diego (CA-11789); University of Missouri, Columbia (CA-12046); Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC (CA-03927); University of Maryland Cancer Center, Baltimore (*D. A. Van Echo*, CA-31983); Columbia University, New York, NY (CA-12011); Cornell Medical Center, New York, NY (CA-07968); Mount Sinai School of Medicine, New York, NY (CA-04457); State University of New York Health Science Center at Syracuse (CA-21060); Central Massachusetts Oncology Group (CA-37135); Dana-Farber Cancer Institute, Boston, MA (CA-32291); Harvard School of Public Health, Boston, MA (*R. Mick*, CA-33601); Massachusetts General Hospital, Boston (CA-12449); McGill Cancer Center, Montreal, Quebec, Canada (CA-31809); Walter Reed Army Medical Center, Washington, DC (*D. J. Perry*, CA-26806); and the University of Chicago, IL (CA-41287).

* *Reprint requests to:* David J. Perry, MD, International Cancer Research Data Bank Branch, International Cancer Information Center, National Cancer Institute, Bldg 82, Rm 115, Bethesda, MD 20892.

had been previously treated, and one had a pretreatment performance status of 3. One additional patient was excluded from the analysis because of inadequate data submission. Thirty-five patients were analyzed for response and survival. Patient characteristics at entry are summarized in table 1.

TABLE 2.—Toxic effects

Toxic effect	No. of patients	%
Myelotoxicity		
Wbc count < 2000/mm^3	19	54
Platelet count < 75,000/mm^3	11	31
Hemoglobin < 8 g/dl	5	14
Fatal pancytopenia, sepsis, bleeding	3	9
Cardiotoxicity		
Supraventricular tachycardia	1	3
Decreased ejection fraction	2	6
Severe nausea, vomiting, diarrhea	1	3
Respiratory failure*	1	3

*Probably pulmonary embolism.

RESULTS

Three patients (9%) achieved partial responses lasting 8.5, > 6.7, and 1.4 months. The median survival for the 35 eligible patients was 3 months.

Toxic effects are summarized in table 2.

DISCUSSION

Deoxydoxorubicin administered at a dose of 30 mg/m^2 iv every 21 days is ineffective in the treatment of primary liver cancer. Additionally, the drug produces excessive hematopoietic and gastrointestinal toxicity, and it is not free of cardiotoxicity (3). Further study of its use in hepatocellular carcinoma at this dose and schedule is not warranted.

REFERENCES

1. ARCAMONE F, PENCO S, REDAELLI S, ET AL. Synthesis and antitumor activity of 4-deoxydaunorubicin and 4′-deoxyadriamycin. J Med Chem 19:1424-1425, 1976.
2. PETO R, PIKE MC, ARMITAGE P, ET AL. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 35:1-39, 1977.
3. RINGENBERG S, PROPERT K, PERRY M, ET AL. Clinical cardiotoxicity of esorubicin: a prospective study with serial gaited heart scans and report of selected cases. Proc ASCO 6:22, 1987.

Oral Urea in Treatment of Liver Metastases From Colorectal Adenocarcinoma[1]

Leslie Levin,[2,*] Walter Kocha,[2] and A. Driedger[3]

There is in vitro and in vivo evidence that tumor cell kill can be achieved by administration of urea (1,2). Following reports that urea was effective in treating superficial cancers (3-6), Danopoulos et al (7) reported complete responses in 15 of 22 patients with hepatic metastases from primary adenocarcinomas treated with oral urea, assuming that high enough concentrations could reach the liver by this route; three of three patients with complete response had colorectal cancer. The present study was performed to evaluate this form of treatment in patients with liver metastases from colorectal cancer who had received no prior treatment. In our study, inclusion criteria were those described by Danopoulos et al (7). Patients were eligible if metastatic disease was confined to the liver but did not exceed one-third of the liver parenchyma and estimated survival was at least 6 weeks; those with ascites or bilirubin of 75 mg/dl were excluded.

Fifteen consecutive patients (9 male and 6 female) were given 18 g of urea daily in six divided doses (8) to assess whether a 20% response rate could be achieved. The product of the two largest perpendicular diameters of the largest tumor on liver scintigraphy was assessed at monthly intervals using standard criteria to define response. Sequential CEA, alkaline phosphatase, and glutamyl transpeptidase levels were also monitored monthly.

The mean age was 64 years (range, 46-79). Performance status (Eastern Cooperative Oncology Group scale) was 0-1 in 14 patients and 2 in one patient; mean time in the study was 2.5 months (range, 1-6). The histological grade of the primary tumor was high grade in 31% of the patients, medium grade in 61%, and low grade in 8%. Treatment was well tolerated.

RESULTS

Tumor progression was evident in all 15 patients, as defined by either a 25% increase in the size of the largest metastasis or the development of new metastases. Although there were decreases in isolated biochemical and CEA measurements, decreasing values of one parameter were never accompanied by a decreasing value of either of the other two parameters. There were no responses in 15 consecutive patients.

CONCLUSIONS

This study was undertaken to investigate reports in the literature that oral urea produces a clinical response in 68% of patients with hepatic metastases from primary adenocarcinomas. Accordingly, 15 consecutive patients were treated with 18 g of urea daily, and response was assessed by sequential liver scintigraphy and chemical measurements. Because no responses were identified in any of the patients examined, it appears that a response rate $> 20\%$ would not be achieved with this treatment ($P < 0.05$). We conclude that this is ineffective therapy.

REFERENCES

1. GLINOS AD, BARDI GN, DERMITZAKI KC, ET AL. Cytokinetic and cytotoxic effects of urea on HeLa cells in suspension cultures. JNCI 71:1211-1219, 1983.
2. ROLL D, SCHWARTZ N, BEN-BASSAT J, ET AL. Effect of uremia on tumor growth in mice. Isr J Med Sci 14:975-978, 1978.
3. DANOPOULOS ED, and DANOPOULOU IE. Urea treatment in skin malignancies. Lancet 1:115-118, 1974.
4. DANOPOULOS ED, CHILARIS GA, DANOPOULOU IE, ET AL. Urea in the treatment of epibulbar malignancies. Br J Ophthalmol 59:282-287, 1975.
5. GHANDI GM, ANASUYA SR, KAWATHEKAR P, ET AL. Urea in the management of advanced malignancies. J Surg Oncol 9:139-146, 1977.
6. DANOPOULOS ED, DANOPOULOU IE, BESBEAS S, ET AL. The effects of urea treatment in combination with curettage in extensive lip cancers. J Surg Oncol 19:127-131, 1982.
7. DANOPOULOS ED, DANOPOULOU IE, BESBEAS S, ET AL. Eleven years experience of oral urea treatment in liver malignancies. Clin Oncol 7:281-289, 1981.
8. GEHAN EA. The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. J Chronic Dis 13:346-353, 1961.

[1] Received Apr 14, 1987; revised Aug 11, 1987; accepted Aug 18, 1987.
[2] Department of Medical Oncology, Ontario Cancer Treatment and Research Foundation, London Regional Cancer Centre, Canada.
[3] Department of Nuclear Medicine, Victoria Hospital, London, Ontario.
* *Reprint requests to:* Leslie Levin, MD, London Regional Cancer Centre, 391 South St, London, Ontario N6A 4G5, Canada.

Continuous Sc Infusion of Metoclopramide for Treatment of Narcotic Bowel Syndrome

Narcotic analgesic agents produce significant effects on the autonomic nervous system (1,2). At the level of the gastrointestinal tract, these drugs may cause a series of functional abnormalities known as the narcotic bowel syndrome (NBS) (3). This syndrome consists of nausea, vomiting, constipation, vague abdominal pain, and episodes of colonic pseudo-obstruction. In narcotic addicts, this syndrome can be treated easily by discontinuation of the narcotic agent. However, in patients with cancer pain, these drugs cannot be discontinued without recurrence of severe pain.

Between June 1985 and August 1986, seven of 191 patients (4%) treated by our group with narcotics were diagnosed as having NBS. All patients had metastatic cancer without abdominal involvement, except for one case of liver metastases. The primary tumor sites were the breast in four patients and the thyroid, lung, and larynx in one patient each. The mean age of the patients was 56 ± 5 years, and four were female. All patients had been receiving oral narcotics (morphine, three; hydromorphone, three; and levorphanol, one) for a mean of 3 ± 2 months, with an equivalent daily dose of 250 ± 170 mg of oral morphine per day. Narcotics were prescribed in all cases for the treatment of cancer pain. All patients developed severe bowel symptoms that required admission to the hospital and parenteral analgesia. None of the patients were receiving phenothiazines or tricyclics. The diagnosis of NBS was based on the criteria described by Sandgren et al (3): nausea and vomiting, mild abdominal discomfort, constipation, abdominal distention due to gas, and at least one episode of colonic pseudo-obstruction. After metabolic abnormalities and mechanical obstruction were ruled out by blood chemistry, physical examination, and abdominal x-rays, all patients started continuous sc infusion of metoclopramide (CSIM) at a dose of 60 mg/day using a disposable portable pump (4). They were monitored daily by one of the authors. Significant improvements in nausea, vomiting, appetite, and abdominal distention were observed in all patients within 72 hours of initiation of the infusion, and they subsequently returned to oral narcotics. The CSIM was continued for 19 ± 6 days, and two patients were discharged home on this treatment. The reasons for discontinuation of CSIM were death unrelated to CSIM (one patient), return to oral metoclopramide (four), discontinuation of narcotics (one), and toxicity (akathisia) after 14 days of infusion (one).

Narcotic analgesic agents have well-known functional effects on the gastrointestinal tract (2). At the level of the upper tract, they cause gastric stasis, a well-documented effect in surgical patients, as well as nausea and vomiting, well-known complications with use of analgesic agents in cancer patients. At the lower level, narcotics cause spastic paresis of the colon (2). Both upper- and lower-level effects are probably mediated at the central nervous system as well as on the walls of the stomach and intestine (2). In addition, patients with advanced cancer frequently show features of cardiovascular (5) or gastric (6) autonomic failure. Autonomic failure can significantly potentiate the untoward effects of narcotics on gastrointestinal motility.

We have previously demonstrated that metoclopramide is readily absorbed when administered as a continuous sc infusion (4). Metoclopramide is known to have strong central and peripheral antidopaminergic effects as well as cholinergic effects, therefore increasing gastrointestinal motility. At this dose level, the tolerance was good, with only one case of extrapyramidal toxicity and akathisia after 14 days of infusion. The diagnosis of NBS is not made frequently in patients with advanced cancer. This may be due to the multiple causes for abnormal bowel function in this population. It is possible that some patients who are considered to have mechanical bowel obstruction, metabolic abnormalities, or unexplained nausea may actually have NBS. In these patients, CSIM can improve symptoms, and in some cases it can allow home discharge.

REFERENCES

1. JAFFE J, and MARTIN W. Opioid analgesics and antagonists. *In* The Pharmacological Basis of Therapeutics (Goodman A, and Gillman A, eds). New York, Macmillan, 1980, pp 494–534.
2. MANARA L, and BIANCHETTI A. The central and peripheral influence of opioids on gastrointestinal propulsion. Annu Rev Pharmacol Toxicol 75:249–273, 1985.
3. SANDGREN JE, MCPHEE MS, NORTON J, ET AL. Narcotic bowel syndrome treated with clonidine. Ann Intern Med 101:331–334, 1984.
4. BRUERA E, BRENNEIS C, MACDONALD RN, ET AL. Continuous subcutaneous infusion of metoclopramide using a disposable portable pump. Ann Intern Med 104:896–897, 1986.
5. BRUERA E, CHADWICK S, FOX R, ET AL. Study of cardiovascular autonomic insufficiency in advanced cancer patients. Cancer Treat Rep 70:1383–1387, 1986.
6. BRUERA E, MACDONALD RN, CATZ Z, ET AL. Chronic nausea and anorexia in patients with advanced cancer: a possible role for autonomic dysfunction. J Pain Symptom Management 2:17–21, 1987.

Eduardo Bruera*
Carleen Brenneis
Mary Michaud
Neil MacDonald[1]

July 1, 1987

[1] Department of Medicine, Cross Cancer Institute, Edmonton, Alberta, Canada.

* *Reprint requests to:* Eduardo Bruera, MD, Department of Medicine, Cross Cancer Institute, 11560 University Ave, Edmonton, Alberta T6G 1Z2, Canada.

Severe and Fatal Toxic Effects Observed in Treatment With High- and Low-Dose Leucovorin Plus 5-Fluorouracil for Colorectal Carcinoma

The Gastrointestinal Tumor Study Group has been conducting a randomized phase III study in advanced measurable colorectal carcinoma comparing 5-fluorouracil (5-FU) alone (500 mg/m^2 by iv bolus on Days 1–5 every 4 wks with escalation as tolerated) versus 5-FU plus high-dose calcium leucovorin (leucovorin at a dose of 500 mg/m^2 iv over 2 hrs + 5-FU at 600 mg/m^2 by iv bolus given 1 hr following initiation of leucovorin, repeated weekly for 6 wks, followed by a 2-wk rest) versus 5-FU plus low-dose leucovorin (leucovorin at 25 mg/m^2 iv over 10 mins + 5-FU at 600 mg/m^2 by iv bolus given 1 hr following initiation of leucovorin, repeated weekly for 6 wks, followed by a 2-wk rest). Unexpectedly severe and fatal toxicity has been observed in the patients receiving high- and low-dose leucovorin plus 5-FU.

Among the patients evaluable for at least one full course of treatment, severe or worse diarrhea has occurred in approximately 25% and 13% of the patients receiving 5-FU with high- and low-dose leucovorin, respectively. A cohort of nine elderly patients (median age, 73 yrs; range, 67–81) experienced fatal toxicity during the initial treatment cycle. The patients developed severe diarrhea with or without nausea and vomiting, leading to dehydration. The majority of these patients had neutropenia and developed fever, and some had documented sepsis. Several of these patients had concomitant stomatitis. All of the patients presented with signs of dehydration, and some had abdominal pain and distention. Three patients developed acute renal failure as the terminal event. Postmortem examinations were performed in two patients. Both patients had evidence of enterocolitis. One patient for whom a complete autopsy report is available had microscopic evidence of hemorrhagic enterocolitis. The second patient had serosanguineous ascites and pleural effusions as well as erosions of the stomach mucosa. Another patient who presented with hypotension, abdominal pain, and tenderness underwent upper gastrointestinal endoscopy, and biopsies were taken from the esophagus and small bowel. Histological examination revealed ileitis, duodenitis, and esophageal ulceration. This patient recovered with vigorous hydration, parenteral hyperalimentation, transfusions, and antibiotics. The clinicopathological picture in these patients, therefore, is toxic enterocolitis with dehydration, and sepsis may have resulted from disruption of the integrity of the mucosal lining. This protocol has been modified subsequently to withhold therapy if any signs of toxicity are observed.

In the phase III study of 5-FU plus leucovorin versus 5-FU alone versus methotrexate plus 5-FU, which was conducted at Roswell Park, diarrhea requiring dose reduction of 5-FU occurred in one-half of the patients assigned to receive 5-FU at a dose of 600 mg/m^2 plus leucovorin at 500 mg/m^2/week for 6 weeks; there was one treatment-related fatality (1).

At the present time, the use of leucovorin in combination with 5-FU is considered to be investigational. The unexpected, severe toxicity observed in both the high- and low-dose leucovorin treatment arms should serve to caution against the use of this combination outside the clinical research setting until further information has been gained about the relative toxicity and therapeutic benefits. This experience underlines the importance of reporting life-threatening and lethal adverse drug reactions that are unexpected or occur at an increased frequency in trials using commercially available agents in a novel, investigational regimen.

REFERENCE

1. PETRELLI N, HERRERA L, STULC J, ET AL. A phase III study of 5-fluorouracil (5-FU) versus 5-FU + methotrexate (MTX) versus 5-FU + high dose leucovorin (CF) in metastatic colorectal adenocarcinoma. Proc ASCO 6:74, 1987.

Jean L. Grem[1,*]
Dale D. Shoemaker[1]
Nicholas J. Petrelli[2]
Harold O. Douglass, Jr[2]

July 22, 1987

[1] Investigational Drug Branch (*J. L. Grem*) and Regulatory Affairs Branch (*D. D. Shoemaker*), Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD.

[2] Department of Surgical Oncology, Roswell Park Memorial Institute, Buffalo, NY.

* *Reprint requests to:* Jean L. Grem, MD, Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Landow Bldg, Rm 4C09, National Institutes of Health, Bethesda, MD 20892.

Carboplatin, Etoposide, and Bleomycin for Treatment of Stage IIC Seminoma Complicated by Acute Renal Failure[1]

Poor renal function in patients with curable cancer needing urgent treatment creates a particular therapeutic dilemma. In a patient with stage IIC seminoma and acute renal failure most probably precipitated by radiocontrast medium, we administered carboplatin and etoposide during the anuric phase. The drug dose was adjusted according to pretreatment creatinine clearance values after re-establishment of diuresis. We added bleomycin to the regimen when there was improvement in renal function. A complete remission was induced after four cycles of chemotherapy and surgery.

CASE REPORT

A 19-year-old student presented with a large left testicular tumor and a massive abdominal tumor. Computerized tomography (CT) examination with radiocontrast enhancement showed a solid mass measuring 21 × 20 cm occupying the entire left side of the abdomen, with obliteration of the left kidney contour. An iv continuous-drip pyelogram showed a nonfunctioning left kidney but a normal right kidney and caliceal structure. The CT examination of the head and chest were negative for metastasis, except for enlarged (1-2-cm) upper mediastinal nodes. Two days later, the patient was totally anuric, and urine output remained < 100 ml for the ensuing 18 days. Blood pressure was 190/100 mm Hg, with grade IV hypertensive retinopathy.

Laboratory data at admission included hemoglobin, 11.6 g/dl; wbc count, 27,400/mm^3 (neutrophils, 66%; bands, 20%; lymphocytes, 7%; monocytes, 6%; and eosinophils, 1%); platelet count, 298,000/mm^3; creatinine, 5.4 mg/dl; uric acid, 11.0 mg/dl; LDH, 5775 units/L (normal, 60–250); beta-human chorionic gonadotropin, 197 ImU/ml (normal, < 5); and alpha-fetoprotein, 1.2 IU/ml (normal, 0.00–6.4).

Hemodialysis was performed daily or every other day for 3 weeks and nifedipine was administered for treatment of hypertension. On the third hospital day, a left testicular tumor measuring 13 × 8 × 5 cm was removed by radical orchiectomy; ureteral stents were placed in both ureters, but no urine flow was observed from either kidney. The histological examination revealed pure seminoma with extensive necrosis.

As shown in table 1, we administered the first chemotherapy cycle (carboplatin at a dosage of 100 mg/m^2 and etoposide at 80 mg/m^2 per day × 3) during the anuric phase. Dialysis was initiated 12 hours after administration of the drugs. The dosage of etoposide was increased to 100 mg/m^2 per day for 5 days in subsequent cycles, and carboplatin was increased to 150, 200, and 250 mg/m^2, corresponding to pretreatment creatinine clearances of 38, 69, and 87 ml/minute, respectively. At the beginning of the second cycle, bleomycin was started at 15 units/week and was continued for 12 weeks.

Levels of beta-human chorionic gonadotropin and LDH returned to normal after the first and second cycles of chemotherapy, respectively. After the fourth cycle, CT examination revealed a residual left abdominal mass measuring 12 × 10 cm. Subsequent surgical exploration of the abdomen disclosed a large retroperitoneal tumor contiguous with major abdominal blood vessels. An atrophied left kidney and left adrenal gland were identified external to the abdominal tumor. The tumor mass and the left kidney were successfully resected and a complete retroperitoneal lymphadenectomy was performed. Histological examination revealed extensive necrosis together with inflammatory cellular reaction. No viable tumor tissue was identified in any of the numerous tissue sections. Moreover, all nodes removed by lymphadenectomy were negative for tumor infiltrate. The postoperative course was uneventful.

TABLE 1.—Chemotherapy regimen

Treatment cycle	Drug*	Dose (mg/m^2)	Day(s)	Pre-Rx creatinine clearance (ml/min)	Wbc count (× 10^3/mm^3)		Platelet count (× 10^3/mm^3)		Hemoglobin (g/dl)		Hair loss	Nausea and vomiting	Infection
					Pre-Rx	Nadir	Pre-Rx	Nadir	Pre-Rx	Nadir			
1	C	100	1	Anuric	10.6	0.9	388	131	9.0	7.8	Partial	Moderate	None
	E	80	1-3										
2	C	150	1†	38	11.0	1.1	575	117	8.9	6.8‡	Total	Moderate	None
	E	100	1-5										
3	C	200	1	69	4.9	1.2	352	131	9.5	7.5	Total	Moderate	None
	E	100	1-5										
4	C	250	1	87	7.0	0.4	447	42	8.7	6.5‡	Total	Moderate	Sepsis§
	E	100	1-5										

*Rx = treatment; C = carboplatin; and E = etoposide.
†Bleomycin was started at dosage of 15 units/wk × 12.
‡Two units of packed rbcs were transfused.
§Blood culture grew *Staphylococcus epidermidis*.

Toxicity from chemotherapy, although significant, was well tolerated. Moderate nausea and vomiting occurred after each dose of carboplatin. Alopecia was severe. A leukopenia nadir of 400–1100 cells/mm^3 and thrombocytopenia of 42,000–131,000/mm^3 occurred 11–16 days after each treatment cycle (table 1). A febrile episode with positive blood culture for *Staphylococcus epidermidis* was documented following the fourth cycle and was treated with appropriate antibiotics. A decrease in hemoglobin (1.2–2.2 g/dl) was observed soon after each chemotherapy cycle, and packed rbc transfusion was administered twice.

COMMENTS

Cisplatin and bleomycin together with either vinblastine or etoposide are the components of two successful treatment regimens for disseminated germ cell tumors including advanced seminomas (1). The known nephrotoxicity of cisplatin makes this drug a poor choice in patients with severe renal failure. Approximately 40% of etoposide is excreted in urine (2); thus, an increased toxicity could be expected if it is administered in the usual dose to the patient with renal failure. Fatal pulmonary toxicity has also been reported in patients with deteriorating renal function receiving bleomycin (3). However, an increase in bleomycin clearance time is reported to occur only when creatinine clearance is reduced to 25–35 ml/minute (4).

Carboplatin has been shown to be an effective agent for the treatment of testicular cancer. Given as a single agent, a dose of 400 mg/m^2 was repeated up to six times in patients with intact renal function (5). Carboplatin differs from cisplatin in its lack of tubular secretion. When administered to patients with normal renal function, it has caused little renal toxicity. Only three of 435 patients entered in phase I–II clinical trials developed grade II–IV renal toxicity (World Health Organization scale) (6). However, in patients with pre-existing renal impairment, the hematologic toxicity is expected to be increased (6).

For this reason, we initiated treatment with reduced doses of carboplatin and etoposide and avoided bleomycin. Carboplatin and etoposide were subsequently increased as renal function improved. Bleomycin was begun only when creatinine clearance surpassed 35 ml/minute. Toxic effects included severe leukopenia and one episode of sepsis at the time of leukopenia nadir. We observed a rapid drop in hemoglobin 10–14 days after each cycle. Although the rbc survival was not measured in our patient, the post-treatment decrease in hemoglobin appears to be due to hemolysis. The binding of carboplatin to rbc membrane has been suspected to cause shortened rbc life span (6).

Our experience with successful treatment of a patient with an advanced seminoma complicated by total renal failure, using carboplatin, etoposide, and bleomycin with dose modification as stated, might be found useful for oncologists facing similar uncommon but critical clinical dilemmas.

REFERENCES

1. WILLIAMS SD, BIRCH R, EINHORN LH, ET AL. Treatment of disseminated germ cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med 316:1435–1440, 1987.
2. SCALZO AJ, COMIS R, FITZPATRICK A, ET AL. VP-16 pharmacokinetics in adults with cancer as determined by a new high-pressure liquid chromatograph (HPLC) assay. Proc ASCO 1:129, 1982.
3. BENNETT WM, PASTORE L, and HOUGHTON DC. Fatal pulmonary bleomycin toxicity in cisplatin-induced acute renal failure. Cancer Treat Rep 64:921–924, 1980.
4. CROOKE ST, COMIS RL, EINHORN LH, ET AL. Effects of variations in renal function on the clinical pharmacology of bleomycin administered as an iv bolus. Cancer Treat Rep 61:1631–1636, 1977.
5. PECKHAM MJ, HORWICH A, and HENDRY WF. Advanced seminoma: treatment with *cis*-platinum-based combination chemotherapy or carboplatin (JM8). Br J Cancer 52:7–13, 1985.
6. Data Brochure: Carboplatin (JM8, CBDA, NSC-241240). Wallingford, CT, Bristol-Myers Co, July 1986, pp 49–69.

Mehdi Farhangi*
Stephen H. Weinstein[2]

July 29, 1987

[1] Carboplatin was supplied by Dr. Michaele Christian, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD.

[2] Division of Hematology/Oncology, Department of Medicine (*M. Farhangi*), and Division of Urology, Department of Surgery (*S. H. Weinstein*), University of Missouri, Columbia.

* *Reprint requests to:* Mehdi Farhangi, MD, Division of Hematology/Oncology, Department of Medicine, School of Medicine, University of Missouri, MA 431C, One Hospital Dr, Columbia, MO 65212.

Ifosfamide/Mesna and Hematuria[1]

Eighty-five patients, ages 1–24 years (median, 12.5), with malignant solid tumors have been treated with 212 courses of ifosfamide (1600 mg/m^2 iv over 15 mins daily × 5) followed by mesna (400 mg/m^2 iv) 4 and 6 hours after ifosfamide (1). Urinalysis was performed daily before each dose of ifosfamide and weekly between treatments, and patients received ifosfamide/mesna when < 50 rbcs/ high-power field were detected in unspun specimens. In the 6 hours after ifosfamide, patients were given 1000 ml/m^2 of 5% dextrose in 0.25 normal saline iv. Patients were then requested to drink 1500–2000 ml/m^2 of additional fluids. Patients unable to consume this volume of fluid orally received supplemental volumes of iv fluids. The number of courses of treatment per patient ranged from one to 12 (median, two). Fifty-seven patients had received cyclophospha-

mide previously, and none had had prior cyclophosphamide-associated hematuria or cystitis; 14 had received prior irradiation to the bladder area.

Fifty-four percent of the treatment courses were delivered in an outpatient clinic. Six treatment courses were abbreviated because of neurotoxicity (two courses), progressive disease (one course), early death from tumor (one), severe nausea and vomiting (one), or hematuria (one), which was defined as > 50 rbcs/high-power field (1,2).

For two of the three patients who developed hematuria, the cause was not related to cystitis. A 16-year-old patient with malignant schwannoma of the chest wall developed hematuria on Day 3 of the first treatment course; he had received no prior bladder irradiation and had spontaneous clearing of rbcs from the urine after cystography. Subsequently, he received ten complete 5-day courses of drugs without recurrence of hematuria; the cause of hematuria was not determined. A 19-year-old patient with atonic bladder secondary to pelvic involvement by osteosarcoma had hematuria associated with the use of a Foley catheter; there was spontaneous resolution of hematuria and no evidence of cystitis at the time of cystoscopy. An 8-year-old boy with multifocal osteosarcoma developed hematuria 1 day following his second 5-day course of ifosfamide/mesna; he had received no prior bladder irradiation and had typical cystoscopic findings of hemorrhagic cystitis. Hematuria cleared spontaneously after 2 days. Disease status had remained stable while he received ifosfamide, and he later received other chemotherapy.

In 13 patients, 5–50 rbcs/high-power field were detected in the urine on one or more occasions. In 69 patients, rbcs were never detected in urine specimens. Late studies of bladder histology and cytology have yet to be performed on patients who have received ifosfamide/mesna.

Thus, only one of 212 courses of ifosfamide/mesna was associated with hemorrhagic cystitis that could be related to treatment. The incidence of hemorrhagic cystitis (0.5%) in our patients compares favorably with other treatment regimens that deliver mesna by prolonged constant infusion or by multiple intermittent bolus doses throughout the days of ifosfamide treatment (3). Without mesna, the reported incidence of hemorrhagic cystitis approximated 50% after treatment with ifosfamide (3). Although microhemoglobinuria (< 50 rbcs/high-power field) can be detected by using sensitive urinary test strips after doses of ifosfamide/mesna (3), this subclinical finding is not associated with any toxic effects of ifosfamide (4,5) and does not require modification of treatment.

Even though mesna has a half-life of 40–140 minutes (4) and ifosfamide oxidation produces substantial amounts of chloroacetaldehyde and has the potential to produce acrolein (5,6), consideration should be given to delivery of mesna following ifosfamide in a dosage and schedule such as that used successfully in this phase II trial. Oral or iv hydration should be given for at least 24 hours after delivery of ifosfamide because of the continued excretion of activated metabolites of ifosfamide when mesna is no longer present in the urine.

REFERENCES

1. PRATT CB, HOROWITZ ME, MEYER WH, ET AL. Phase I trial of ifosfamide in children with malignant solid tumor. Cancer Treat Rep 71:131–135, 1987.
2. PRATT CB, GREEN AA, HOROWITZ ME, ET AL. Central nervous system toxicity following the treatment of pediatric patients with ifosfamide/mesna. J Clin Oncol 4:1253–1261, 1986.
3. BRADE WP, HERDRICK K, and VARINI M. Ifosfamide—pharmacology, safety and therapeutic potential. Cancer Treat Rev 12:1–47, 1985.
4. GOREN MP, WRIGHT RK, HOROWITZ ME, ET AL. Ifosfamide-induced subclinical tubular nephrotoxicity despite mesna. Cancer Treat Rep 71:127–130, 1987.
5. GOREN MP, WRIGHT RK, PRATT CB, ET AL. Potentiation of ifosfamide neurotoxicity, hematotoxicity, and tubular nephrotoxicity by prior cisplatin therapy. Cancer Res 47:1457–1460, 1987.
6. COLVIN M. The comparative pharmacology of cyclophosphamide and ifosfamide. Semin Oncol 9(suppl 1):2–7, 1982.

Charles B. Pratt*
Marshall P. Goren[2]

August 3, 1987

[1] Supported by Public Health Service grants CA-23099 and CA-21765 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and by the American Lebanese Syrian Associated Charities.

[2] Departments of Hematology/Oncology (*C. B. Pratt*) and Pathology and Laboratory Medicine (*M. P. Goren*), St. Jude Children's Research Hospital, Memphis, TN.

**Reprint requests to:* Charles B. Pratt, MD, Department of Hematology/Oncology, St. Jude Children's Research Hospital, PO Box 318, Memphis, TN 38101.

Generation of Dose Intensity-Response Data Suggested for Drug Studies

In the June 6, 1987, volume of *Cancer Treatment Reports*, Slayton et al reported on behalf of the Gynecologic Oncology Group that etoposide had minimal activity (6% partial response rate) in the treatment of advanced or recurrent mixed mesodermal sarcomas of the uterus. The authors were careful to qualify their conclusion as being restricted to the dose and schedule tested. Toxicity was mild to moderate.

I wonder if the authors would consider whether this study and others like it should use a different design and should test not one dose intensity (75 mg/m^2/wk), but a range including higher dose intensities. Only by generating dose intensity-response lines will we determine the true usefulness of this drug in uterine sarcoma and of other drugs in other diseases. In diseases in which etoposide is active (eg, small cell lung cancer),

dose intensities in the order of 100–150 mg/m^2/week must be exceeded before the response rate is appreciable, and then the response rate rises quickly with further increments of dose intensity. Furthermore, within limits, these higher dose intensities might be achievable without necessarily triggering commensurate increases in toxicity, providing treatment scheduling is taken into account.

William M. Hryniuk[1,*]

August 14, 1987

[1] Henderson Clinic, The Ontario Cancer Treatment and Research Foundation, Hamilton Regional Cancer Centre, Canada.

* *Reprint requests to:* William M. Hryniuk, MD, Henderson Clinic, The Ontario Cancer Treatment and Research Foundation, Hamilton Regional Cancer Centre, 711 Concession St, Hamilton, Ontario L8V 1C3, Canada.

ANNOUNCEMENTS

Association for Brain Tumor Research Opens Applications for 1988 Fellowships

The Association for Brain Tumor Research, Chicago, is now accepting applications for fellowships from postdoctoral candidates whose intent is to pursue a career in brain tumor research. Preference will be given to MD's who are US citizens or permanent residents of the U.S., seeking research training that will enable them to pursue careers as clinical investigators.

AFBTR fellowships offer an award of $18,000 per annum plus a $2000 annual travel allowance for a period of 2 years, with a third-year-renewable option. A presentation to the AFBTR Board of Directors in Chicago is required during the second year of the fellowship.

Applications must be submitted by the sponsoring program director, and deadline for completed applications, including letters of recommendation and attachments, is January 8, 1988. Awards will be announced by April 1, 1988, for fellowships to begin July 1, 1988.

Application forms may be obtained from the Association for Brain Tumor Research, 2910 W Montrose Ave, Chicago, IL 60618, and completed applications should be mailed to the same address.

For additional information, contact: Association for Brain Tumor Research, 2910 W Montrose Ave, Chicago, IL 60618-1404 (telephone: 312-286-5571).

4th Annual Recent Advances in Occupational Cancer

San Francisco, California, December 3-5, 1987

For further information, contact: Postgraduate Programs, Department of Medicine, M979, 505 Parnassus Ave, Box 0120, University of California, San Francisco, CA 94143-0120 (telephone: 415-476-5208).

International Workshop on Monokines and Other Non-Lymphocytic Cytokines

Hilton Head Island, South Carolina, December 6–10, 1987

For further information, contact: Reticuloendothelial Society c/o Dr. Sherwood M. Reichard, Medical College of Georgia, Augusta, GA 30912 (telephone: 404-828-2601).

Symposium on Interferons and Tumor Necrosis Factors—Advances in Clinical Research

Brussels, Belgium, December 9, 1987

For further information, contact: Ms. D. Eeckhoudt, Executive Secretary, EORTC Data Center, Blvd de Waterloo 125, 1000 Brussels, Belgium (telephone: 2-539-28-05).

R. Livingston Ireland Cancer Center Symposia: Management of Hematologic Malignancies

Cleveland, Ohio, January 30, 1988

For further information, contact: Barbara Guy, PhD, Assistant to the Director, R. Livingston Ireland Cancer Center, University Hospitals of Cleveland, Case Western Reserve University, 2074 Abington Rd, Cleveland, OH (telephone: 216-844-7856).

Second International Congress on Neo-Adjuvant Chemotherapy

Paris, France, February 4–6, 1988

For further information, contact: S.O.M.P.S., Hôpital de la Salpétrière, 47 boulevard de l'Hôpital, 75651 Paris Cédex 13, France.

Comprehensive Care of the AIDS Patient: A Workshop

San Francisco, California, February 12–13, 1988

For further information, contact: University of California Extended Programs in Medical Education, Rm U-569, San Francisco, CA 94143–0742 (telephone: 415-476-4251).

R. Livingston Ireland Cancer Center Symposia: Cancer In Women: Diagnosis and Management

Cleveland, Ohio, February 27, 1988

For further information, contact: Barbara Guy, PhD, Assistant to the Director, R. Livingston Ireland Cancer Center, University Hospitals of Cleveland, Case Western Reserve University, 2074 Abington Rd, Cleveland, OH (telephone: 216-844-7856).

Third International Conference on Adjuvant Therapy of Breast Cancer

St. Gallen, Switzerland, March 3–5, 1988

For further information, contact: Secretariat Prof. H. J. Senn, MD, Department of Medicine C, Oncology Center, Kantonsspital, CH-9007 St. Gallen, Switzerland (telephone: 719-219-KSSG CH).

Bone Marrow Transplantation: Current Controversies

Tamarron, Colorado, March 6–12, 1988

For further information, contact: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024 (telephone: 213-206-6292).

2nd Annual Infusional Chemotherapy Symposium

Boston, Massachusetts, April 7–8, 1988

For further information, contact: Ms. Barbara McConnell, The Cancer Center, 125 Parker Hill Ave, Boston, MA 02120 (telephone: 617-739-6605 or 617-738-7368).

R. Livingston Ireland Cancer Center Symposia: Recent Advances in Non-Melanoma Skin Cancer

Cleveland, Ohio, April 16, 1988

For further information, contact: Barbara Guy, PhD, Assistant to the Director, R. Livingston Ireland Cancer Center, University Hospitals of Cleveland, Case Western Reserve University, 2074 Abington Rd, Cleveland OH (telephone: 216-844-7856).

International Symposium: The Expanding Role of Folates and Fluoropyrimidines in Cancer Chemotherapy

Buffalo, New York, April 28–29, 1988

For further information, contact: Gayle Bersani, RN, Coordinator of Continuing Education Programs, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263 (telephone: 716-845-2339).

International Symposium on Therapeutic Progress in Urological Cancers

Paris, France, June 29–July 1, 1988

For further information, contact: Dr. Gerald P. Murphy, Professor of Urology, School of Medicine, State University of New York at Buffalo, 139 Parker Hall, Buffalo, NY 14214 (telephone: 716-831-2338).

Second International Congress on Cancer Pain

Rye, New York, July 14–17, 1988

For further information, contact: Mary Callaway, Executive Director, Memorial Sloan-Kettering Cancer Center, Box 52, 1275 York Ave, New York, NY 10021.

Third International Conference on Drug Absorption

Edinburgh, Scotland, September 28–30, 1988

For further information, contact: Dr. Ian Sword, Inveresk Research International Ltd, Musselburgh EH21 7UB, Scotland (telephone: 031-665-6881).

Cancer Treatment Reports

ORIGINAL ARTICLES

997 Dacarbazine, Vindesine, and Cisplatin Combination Chemotherapy in Advanced Malignant Melanoma: A Phase II Study

1001 Continuous 5-Day Infusion of Vinblastine for Percutaneous Hepatic Arterial Chemotherapy for Metastatic Breast Cancer

1007 Randomized, Double-Blind, Cross-Over Study Comparing Prochlorperazine and Lorazepam With High-Dose Metoclopramide and Lorazepam for the Control of Emesis in Patients Receiving Cytotoxic Chemotherapy

1013 Preliminary Report on the Treatment of Esophageal Cancer by Intraluminal Microwave Hyperthermia and Chemotherapy

1021 Comparison of the Actions of the Antiprogestin Mifepristone (RU486), the Progestin Megestrol Acetate, the LHRH Analog Buserelin, and Ovariectomy in the Treatment of Rat Mammary Tumors

1029 High-Dose Pulse Chlorambucil in Advanced, Low-Grade Non-Hodgkin's Lymphoma

1033 Improved Survival of Infants Less Than 1 Year of Age With Acute Lymphoblastic Leukemia Treated With Intensive Multiagent Chemotherapy

1039 Pediatric Phase I Trial of Carboplatin: A Childrens Cancer Study Group Report

1043 Pharmacokinetics of Continuous-Infusion High-Dose Thiotepa

1049 Carboplatin or Iproplatin in Advanced Non-Small Cell Lung Cancer: A Cancer and Leukemia Group B Study

1053 Selective Treatment of Metastatic Lymph Nodes With Combination of Local Hyperthermia and Temperature-Sensitive Liposomes Containing Bleomycin

1061 Treatment Evaluation in Active Control Studies

1067 Inadequacy of Predicted Creatinine Clearance as Guide to Chemotherapy

1071 Management of Learned Food Aversions in Cancer Patients Receiving Chemotherapy

REVIEW ARTICLE

1079 How Large Should a Phase II Trial of a New Drug Be?

BRIEF REPORTS

1087 Chemotherapy of Adult Soft Tissue Sarcoma With Combination of Doxorubicin and Methotrexate

1089 Inhibitory Action of Flurbiprofen and Mopidamole on Tumor Lung Metastasis Formation in Mice

1091 Oral Gestrinone: A Novel Antiprogestin With No Antitumor Activity in Endocrine-Sensitive Breast Cancer

1093 Facilitation of Emergence of Multidrug-Resistant State by Alteration of Tumor Environment: Implications From Competitive Ecology Models

CLINICAL TRIALS SUMMARIES

1095 Phase II Trial of Diaziquone in Patients With Refractory and Relapsing Multiple Myeloma: A Southwest Oncology Group Study

1097 Phase II Study of Isotretinoin in the Treatment of Advanced Non-Small Cell Lung Cancer

1099 Phase II Study of Caracemide in Advanced or Recurrent Non-Small Cell Lung Cancer

1101 Phase II Trial of Bisantrene in Hepatocellular Carcinoma: A Southwest Oncology Group Study

1103 Phase II Trial of Ifosfamide/Mesna in Metastatic Adult Renal Carcinoma

1105 Phase II Study of Spirohydantoin Mustard for the Treatment of Recurrent Malignant Gliomas

1107 Phase II Trial of Prednimustine as First-Line Chemotherapy in Patients With Advanced Breast Cancer

1109 Phase II Study of Mitoxantrone in Untreated and Previously Minimally Treated Patients With Metastatic Soft Tissue Sarcomas

1111 Phase II Study of Fludarabine Phosphate in Previously Untreated Patients With Hepatoma: A Southwest Oncology Group Study

1113 Continuous-Infusion Amsacrine in Patients With Refractory Acute Myelogenous Leukemia

1115 Ifosfamide Plus 5-Fluorouracil for Treatment of Adenocarcinoma of the Pancreas

1117 Phase II Study of Deoxydoxorubicin in Patients With Advanced Liver Cancer

1119 Oral Urea in Treatment of Liver Metastases From Colorectal Adenocarcinoma

LETTERS

1121 Continuous Sc Infusion of Metoclopramide for Treatment of Narcotic Bowel Syndrome

1122 Severe and Fatal Toxic Effects Observed in Treatment With High- and Low-Dose Leucovorin Plus 5-Fluorouracil for Colorectal Carcinoma

1123 Carboplatin, Etoposide, and Bleomycin for Treatment of Stage IIC Seminoma Complicated by Acute Renal Failure

1124 Ifosfamide/Mesna and Hematuria

1125 Generation of Dose Intensity-Response Data Suggested for Drug Studies

NIH Publication No. 87-22

November 1987